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Correlations between Relative Interstitial Volume of the Renal Cortex and Serum Creatinine Concentration in Minimal Changes with Nephrotic Syndrome and in Focal Sclerosing Glomerulonephritis

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Summary. Morphometric investigations were performed in 33 biopsies with minimal proliferative intercapillary glomerulonephritis with nephrotic syndrome (MPI with NS, minimal changes with nephrotic syndrome) and in 65 biopsies with focal sclerosing glomerulonephritis (FGS). Both diseases are, in our opinion, variants of a single entity. Positive significant correlations (corresponding to linear and parabolic functions) between the relative interstitial volume of the renal cortex and serum creatinine concentration at the time of biopsy could be found. No correlations were observed between percentage of glomeruli affected by segmental and focal sclerosis in FGS and relative interstitial volume, or the percentage of involved glomeruli and serum creatinine concentration. The enlargement of the cortical interstitium by fibrosis may lead to a narrowing of the postglomerular vessels, to an elevation of the postglomerular flow resistance and to a slowing of the glomerular blood flow. In this way the filtrate of the glomerulus could be reduced and lead to a elevation of the serum creatinine concentration. Alternatively the observed tubular atrophy in fibrotic areas – caused by malnutrition or inactivity – could impair the tubular capacity of resorption. This may lead to a reduction of the glomerular filtrate by the so called Thurau mechanism in the case of interstitial fibrosis.

Key words: Focal sclerosing GN – Minimal changes with nephrotic syndrome – Creatinine concentration – Rel. interstitium volume.

Introduction

Investigations on correlations between relative interstitial volume and serum creatinine concentration at the time of biopsy in inflammatory and noninflamma-

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tory glomerular diseases showed that the serum creatinine concentration is more influenced by interstitial fibrosis than by the severity of glomerular lesions (Bohle et al., 1977 a and b; Fischbach et al., 1977; Mackensen et al., 1977; Grund et al., 1977).

The present paper attempts to determine whether there are similar relations in minimal changes with the nephrotic syndrome, which we call minimal proliferative intercapillary glomerulonephritis with NS (MPI with NS) resp. focal sclerosing glomerulonephritis (FGS).

In MPI with NS (Synonyms: minor or minimal lesion (Kincaid-Smith and Hobbs, 1972), minimal glomerulitis (Thoenes, 1973), minimal sclerosing glomerulonephritis (Zollinger, 1971), minimal proliferative intercapillary glomerulonephritis, MPI (Bohle et al., 1969) the permeability of the glomerular capillaries for protein is enormously increased and leads to the nephrotic syndrome. Light microscopically proliferation of the cells in mesangial position can be established only by morphometric methods (Wehner, 1974; Bohle et al., 1969). Electron microscopy shows a flattening and fusing of the foot processes of the glomerular epithelial cells.

In focal sclerosing glomerulonephritis (Synonyms: segmental and focal hyalinosis (Habib, 1970; Habib and Gubler, 1971), segmental and focal hyalinosis, and segmental and focal fibrosis or sclerosis (Kincaid-Smith and Hobbs, 1972), focal segmental sclerosing glomerulonephritis (Rumpelt and Thoenes, 1972; Thoenes, 1973), focal glomerular sclerosis (NAGI et al., 1971), focal sclerosing glomerulonephropathy with segmental hyalinosis (Hyman et al., 1973)) the unaffected glomeruli resemble those in MPI with NS light- and electronmicroscopically. Thus FGS is also a diffuse glomerular disease (Rumpelt and Thoenes, 1974; Bohle et al., 1974), which may be associated with segmental and focal changes in a greater or lesser number of glomeruli in the course of the disease. These changes first predominate in the juxtamedullary glomeruli and then expand to the middle and external zone of the renal cortex. The so called hyalinose ségmentale et focale (Habib, 1970) is characterized by a segmental thickening of the basement membrane, enlargement of the matrix of the mesangium cells, subendothelial deposits of plasma substances, further fatty degeneration of the endothelial cells and coalescence of these areas with Bowman's capsule (Bohle et al., 1977). At the endstage of the disease these foci can cicatrize or lead to a complete hyalinization of the glomerulus.

Materials and Methods

From 293 cases of MPI with NS 33 biopsies were investigated, and out of 298 with FGS 65 biopsies were examined, all contained at least 5 glomeruli,. All biopsies with a serum creatinine concentration above 1.2 mg/100 ml and some of the cases with normal serum creatinine concentration ($\leqq$1.2 mg/100 ml) and a normal interstitium were investigated.

The biopsies were fixed in 4% formalin solution (pH 7.4). 5–8 µm thick paraffin sections, stained by Goldner-trichrome or PAS were examined using the Reichert visopan projection microscope (objective 10/0.2, magnification 125:1).

In the renal cortex 5 projection fields per kidney were measured under a lattice of 1 cm, discriminating between interstitium, epithelia and lumina, neglecting large vessels and glomeruli.

Focal changes were evaluated according to their respective proportions. The values obtained – relative interstitial volumes- were correlated with the serum creatinine concentration at the time of biopsy. We determined the correlation-coefficient r, the error probability α (from the t-test) and the equations of regression for linear, parabolic and exponential functions. Similar measurements were made on 20 control kidneys with normal function.

Rank correlations were determined for the percentage of glomeruli affected by focal sclerosis and the relative interstitial volume with respect to serum creatinine concentration. Furthermore the mean and standard deviation of the relative interstitial volume, age, blood pressure, serum protein, proteinuria and serum creatinine of the 293 cases with MPI with NS *resp.* the 298 cases with FGS were calculated. The *t*-test was used to check the significance of differences between these two diseases.

Results

In MPI with NS and in FGS there are significant correlations between relative interstitial volume and serum creatinine concentration at the time of biopsy (Figs. 1 and 2, Tables 1 and 2).

In MPI with NS serum creatinine concentrations of a maximum of 8.8 mg/100 ml and relative interstitial volumes up to 42 Vol% were observed, even in cases of recurring nephrotic syndrome. In FGS, however, serum creatinine concentrations up to 8.8 mg/100 ml and relative interstitial volumes up to 54 Vol% were found.

Cases with acute renal failure at the time of biopsy were not used for calculation in both diseases (5 cases of MPI with NS, 5 cases of FGS). In the cases of acute renal failure – even if combined with glomerulonephritides –

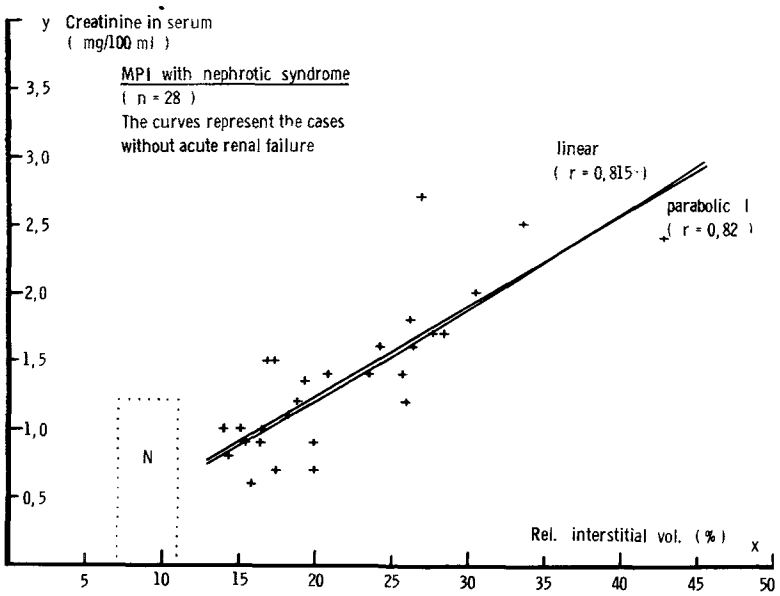

Fig. 1. Correlations between relative interstitial volume (x-axis) and serum creatinine concentration (y-axis) at the time of biopsy in MPI with NS · *N* Range of normal kidneys

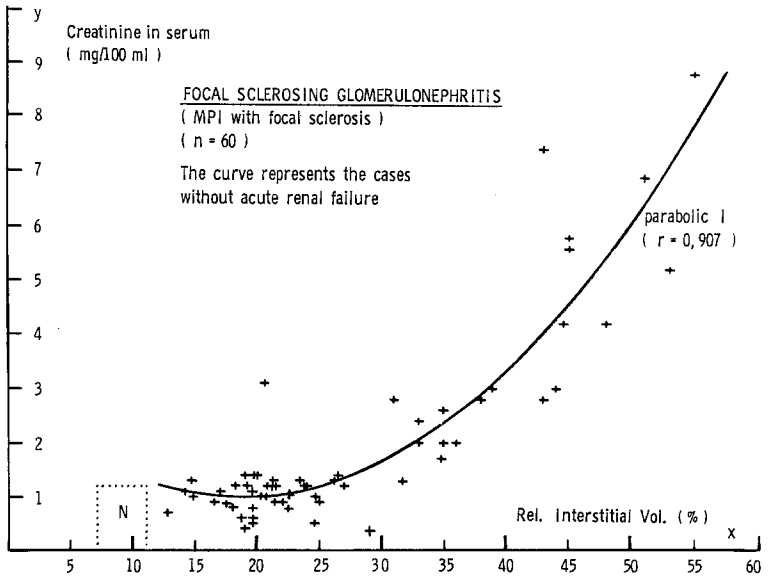

Fig. 2. Correlations between relative interstitial volume (x-axis) and serum creatinine concentration (y-axis) at the time of biopsy in FGS·*N* Range of normal kidneys

Table 1. Analysis of regression and correlation between relative interstitial volume and serum creatinine concentration

MPI with NS (without a.r.f.)

x/y	Function	Correlation coefficient	Error probability α	t=
linear (lin/lin)	$y=0.076+0.065x$	0.815	all $\leqq 0.001$	7.18
Parabolic I	$y=0.53+0.1x-0.0007x^2$	0.820		7.33
Exponential (lin/log)	$y=0.46\cdot e^{0.045x}$	0.784		6.43
Parabolic II (power log/log)	$y=0.045\cdot x^{0.63}$	0.796		6.54

Means: $\bar{x}$ (interstitium)	22.06 ± 6.76 Vol%	
$\bar{y}$ (ser. creatinine)	1.37 ± 0.54 mg/100 ml	n=28
Age of patients	$32.1\ \pm16.9$ years	

there are no correlations between serum creatinine concentration at the time of biopsy and relative interstitial volume (Bohle et al., 1977).

In FGS no correlations (rank-correlations, $r_s=0.21$) between the percentage of glomeruli affected by segmental and focal sclerosis and relative interstitial volume were found (Fig. 3), even if FGS is combined with totally hyalinized glomeruli. Correlations between involved glomeruli and serum creatinine concentration at the time of biopsy were also not significant ($r_s=0.12$) (Fig. 4).

There is no difference between MPI with NS and FGS with respect to degree of proteinuria and hypoproteinemia. The means of the parameters: age,

Table 2. Analysis of regression and correlation between relative interstitial volume and serum creatinine concentration at the time of biopsy

FGS (without acute renal failure)

x/y	Function	Correlation coefficient	Error probability α	t=
Linear (lin/lin)	$y=1.91+0.141\times$	0.849		12.2
Parabolic I	$y=2.82-0.19\times+0.005\times^2$	0.907	all $\leqq 0.0001$	16.4
Exponential (lin/log)	$y=0.32\cdot e^{0.056}$	0.835		11.55
Parabolic II (power log/log)	$y=0.009\cdot\times^{1.56}$	0.791		9.9

Means: $\bar{x}$ (interstitium) 27.47 ± 10.8 Vol%
$\bar{y}$ (ser.creatinine) 1.97 ± 1.81 mg/100 ml $n=60$
Age of patients 34.7 ± 17.17 years

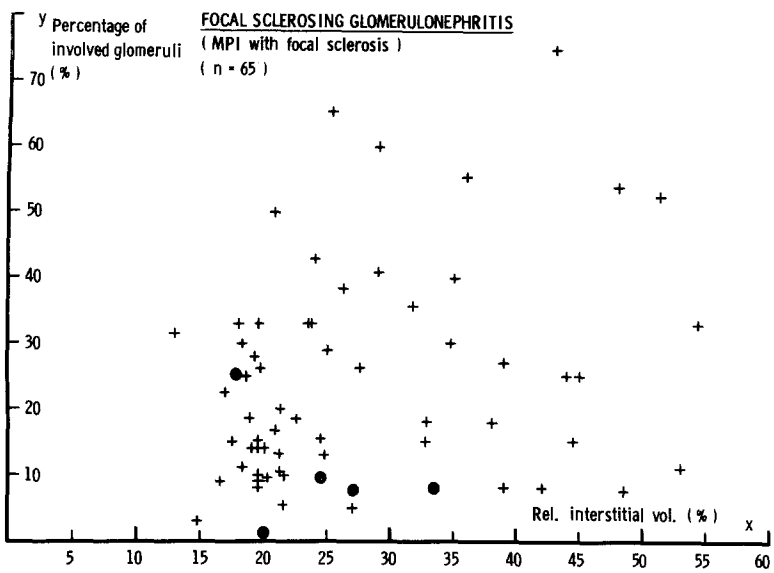

Fig. 3. Correlations between percentage of glomeruli affected by segmental and focal sclerosis and relative interstitial volume in FGS. + without a.r.f., $n=60$ (the percentage of partly hyalinized glomeruli was neglected in this figure). ● with a.r.f., $n=5$

blood pressure and serum creatinine concentration in FGS – however – exceed that of MPI with NS significantly (Table 3).

Discussion

The present investigations show similar positive significant correlations between relative interstitial volume and serum creatinine concentration at the time of biopsy in MPI with NS and FGS, as in formely investigated inflammatory

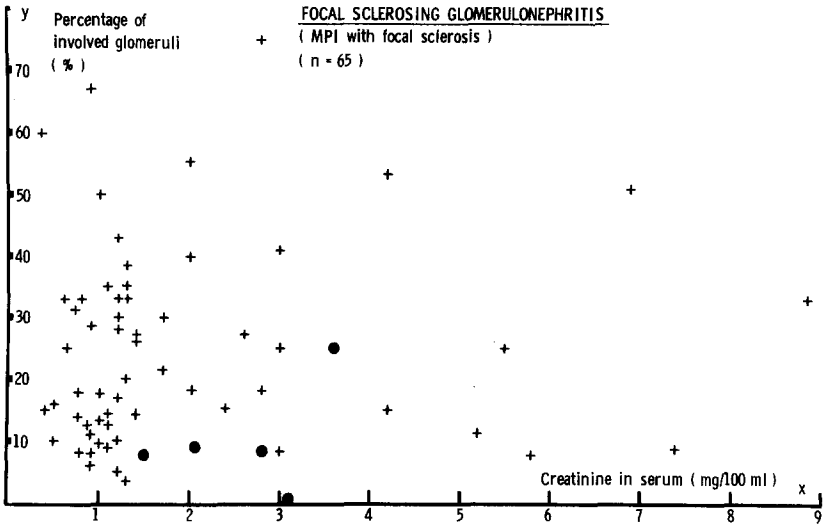

Fig. 4. Correlations between percentage of involved glomeruli and serum creatinine concentration at the time of biopsy (same symbols as in Fig. 3)

Table 3. Analysis of clinical data in MPI with NS and FGS. There are different quantities of values, because the information was not complete in all cases

	FGS	MPI with NS	*t*	
Age	31.9 ± 16.8 n = 298	24.1 ± 17.1 n = 293	5.6	s
Sex (♂:♀)	1:0.75 n = 298	1:0.64 n = 299		
Mean blood pressure (p syst. + 2p diast./3)	116.1 ± 18.1 n = 237	104.3 ± 15.0 n = 219	7.54	s
Serum protein (g/100 ml)[a]	5.31 ± 1.27 n = 194	5.38 ± 1.30 n = 182	0.552	∅
Proteinuria (g/die)[a]	7.11 ± 6.39 N = 242	7.54 ± 12.7 n = 178	0.46	∅
NS[a b]	87% n = 100	95% n = 100		
Relative interst. volume (Vol. %)	27.38 ± 10.52 n = 65	22.70 ± 8.19 n = 33	2.23	s
Serum creatinine concentration (mg/100 ml)	1.58 ± 1.31 n = 209	1.04 ± 0.51 n = 221	5.65	s

∅ = no significance
s = significant
[a] = at the time of biopsy
[b] = data taken from Bohle et al. (1974)

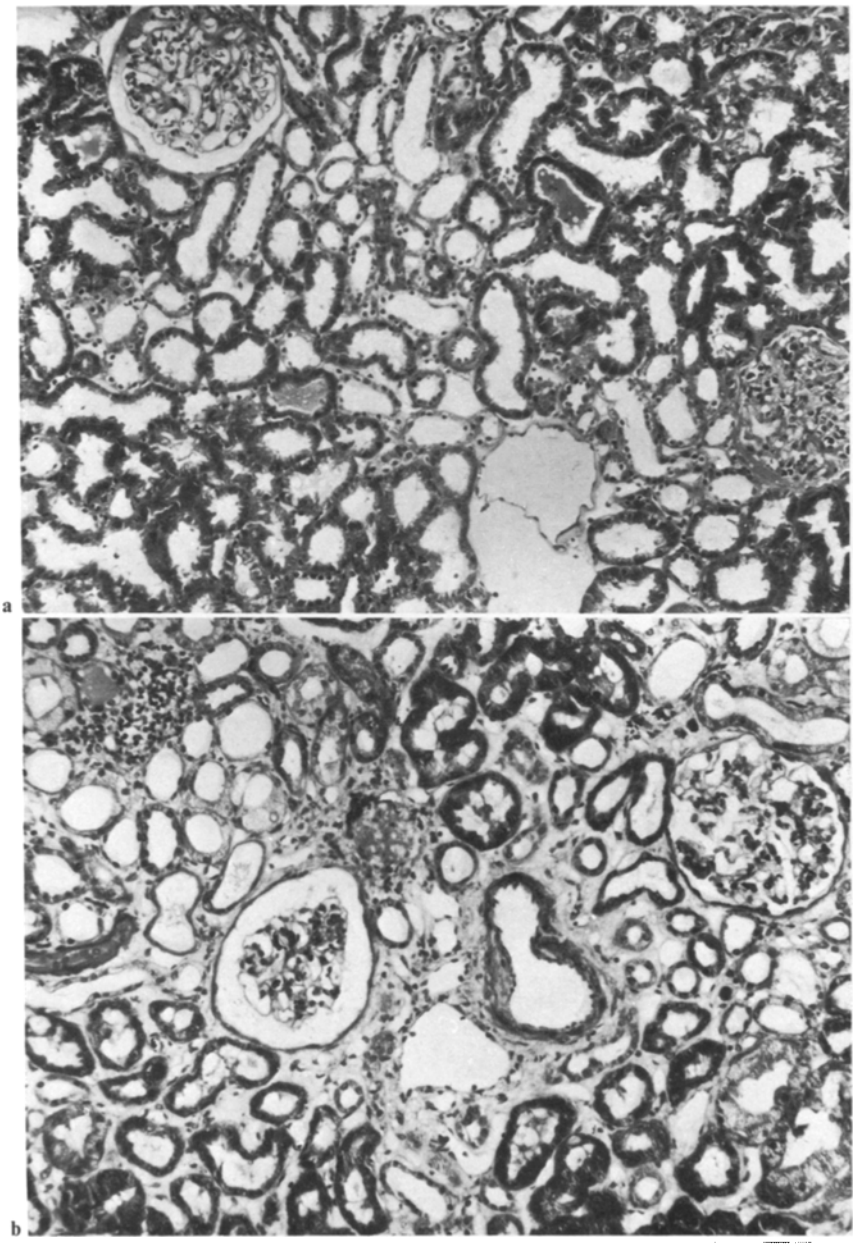

Fig. 5. a 77/2/1791 MPI with recurring NS since 12 years, Cr. 1.0 mg/100 ml not enlarged rel. interst. volume. Goldner-trichrome 144:1. **b** 76/5/573 MPI with NS, Cr. 3.6 mg/100 ml, rel. interst. volume markedly enlarged. Goldner-trichrome 144:1. This case is not plotted in Figure 1

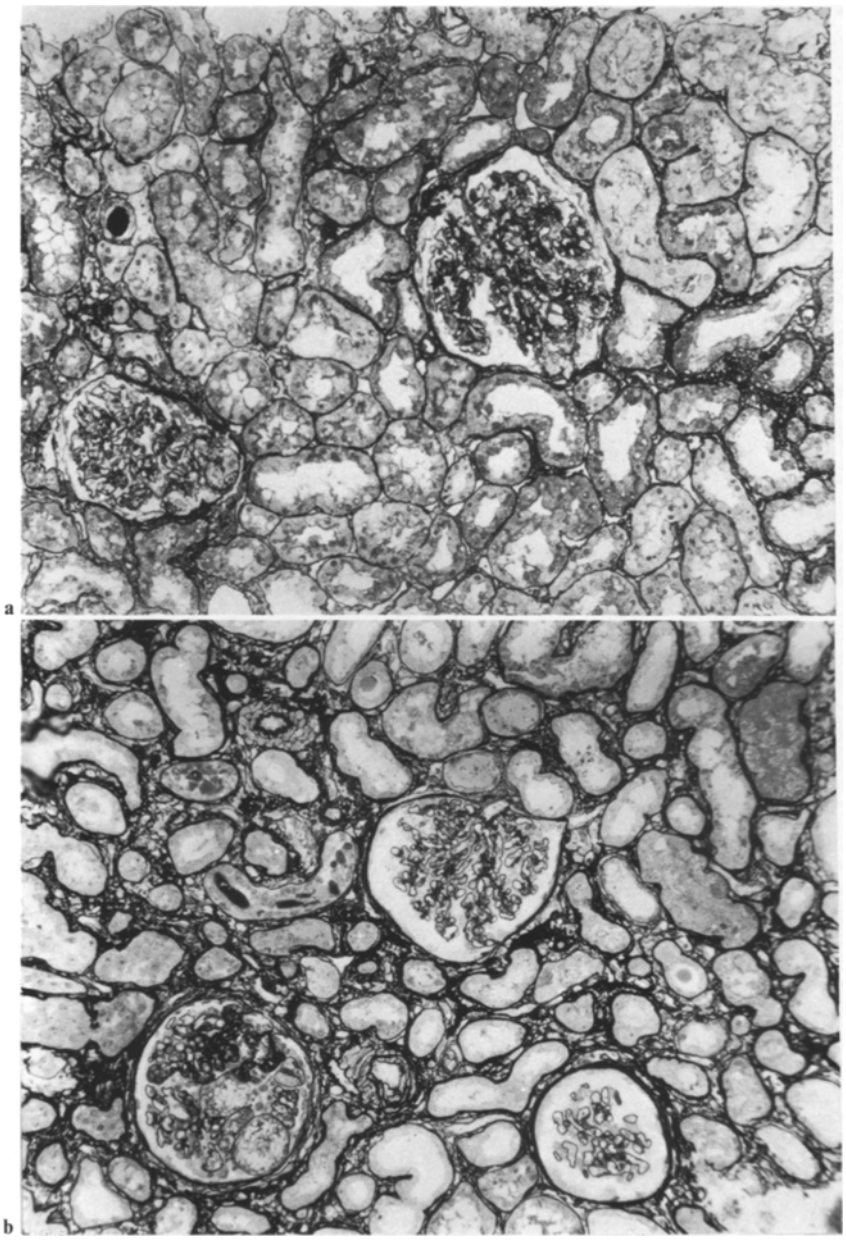

Fig. 6. a 74/7/613 FGS with NS, Cr. 1.3 mg/100 ml, rel.interst. volume nearly normal. Semithin silver-impregnation after MOVAT 144:1. **b** 71/7/1455 FGS with NS, Cr. 5.5 mg/100 ml, rel. interst. volume markedly enlarged, semithin silver impregnation after MOVAT 144:1

and noninflammatory glomerular diseases (Bohle et al., 1977 a and b; Fischbach et al., 1977; Mackensen et al., 1977).

In MPI with NS, however, interstitial fibrosis (Fig. 5 a and b) combined with elevated serum creatinine concentration is observed only half as frequently as in FGS (Fig. 6a and b). Relative interstitial volumes up to 54 Vol% with serum creatinine concentrations up to 8.8 mg/100 ml could be found in FGS, while in MPI with NS – except in the cases with acute renal failure (a.r.f.) – relative interstitial volumes only up to 42Vol% with serum creatinine concentrations up to 2.8 mg/100 ml were observed. The significant enlargement of the relative interstitial volume in FGS – compared with MPI with NS – seems not to be influenced nor caused by focal and segmental lesions in different numbers of affected glomeruli. Not enlarged relative interstitial volume and not elevated serum creatinine concentrations can be found in cases with many alterated, almost totally hyalinized glomeruli or vice versa (Figs. 3 and 4).

In agreement with Thoenes and Rumpelt (1974) it was shown by electron microscopy that in MPI with NS as well as in FGS all glomeruli are affected (Bohle et al., 1974).

Fahr has reported on an enlargement of the interstitium in FGS, the so called "lipoid nephrosis" (Fahr, 1925; Rich, 1957). The expanding of the interstitium is said to cause a change in the character of this disease. "In the masses of the granulation tissue produced rests of tubules can be found, the glomeruli look remarkably normal".

In focal glomerulosclerosis (Churg et al. (1970) interstitial fibrosis often has been described (McGovern, 1964; Churg et al., 1970; White et al., 1970; Habib, 1973; Hyman and Burkholder, 1973) and illustrated (Rumpelt and Thoenes, 1972).

Newman et al. (1976) tried to correlate morphological glomerular and non glomerular changes in FGS with functional disturbances of the kidney using a non specified semiquantitative method. In some cases closer correlations could be found between severity of non glomerular than glomerular lesions and renal function.

The increase of the renal interstitium in a patient with FGS – without pyelonephritis –, who was repeatedly biopsied, was emphasized by McGovern (1964). Cases with rapidly developing renal insufficiency showed more distinct interstitial changes than glomerular alterations. In one case, published three years later, the worse prognosis of a glomerular disease was attributed – without reflecting upon its cause and its importance for the development of renal insufficiency – to the increase in interstitial fibrosis (McGovern, 1967). Interstitial fibrosis in FGS is thought to be an indicator of a damage of the whole nephron with secondary ischemic and metabolic alterations of the glomeruli, tubules and interstitium (Hyman and Burkholder, 1973). The functional impairment of renal function is shown to be connected with interstitial enlargement – provided that the enlargement is caused by interstitial fibrosis, i.e. increase of collagen fibres (Fig. 5a and b, Fig. 6a and b) (Bohle et al., 1977 a and b; Fischbach et al., 1977; Mackensen et al., 1977).

In cases of acute renal failure, in which interstitial edema is observed in the stage of oligo-anuria, renal function does not recover if persisting interstitial edema develops into sclerosis of the organ (Bohle et al., 1977 a and b).

Whether the interstitial fibrosis in MPI with NS or FGS is caused by an acute renal failure developing during the course of NS cannot be answered yet. It is striking however that there were 5 resp. 5 cases with clinically ensured acute renal failure at the time of biopsy in the entire series. These cases may point to the possibility that MPI with NS and FGS is accompanied by acute renal failure more often than expected or discovered (Bohle et al., 1974). These two diseases seem to be variants of a single entity according to Kashgarian et al. (1974), Siegel et al. (1974), Habib and Gubler (1971), Habib (1973), McGovern (1964) Hamburger et al. (1973), in contrast to Velosa et al. (1975), Nagi et al. (1971), Newman et al. (1976).

An acute renal failure with interstitial edema does not have to be the exclusive cause for the interstitial fibrosis. In previously investigated diseases (Bohle et al., 1977 a and b; Grund et al., 1977) different degrees of interstitial fibrosis were found with the corresponding serum creatinine concentration in differing frequency. An acute renal failure was seldom observed.

The glomerular filtration process seems to be more influenced by interstitial fibrosis than expected. Possibly a narrowing of the postglomerular capillaries by interstitial fibrosis could impair glomerular function. Postglomerular flow resistance and glomerular blood pressure may thus be raised. In spite of an increasing filtration fraction the slowing of the glomerular blood flow may reduce the effective glomerular filtration rate and thus result in an increased serum creatinine concentration.

However tubules appear atrophied in fibrotic areas in these two glomerular diseases. It is not known whether this tubular atrophy is caused by malnutrition or whether it is a sign of inactivity. We believe it is probable that the tubular resorptive capacity of atrophied tubules is impaired – as in cases with acute renal failure. The resulting reduction of the glomerular filtrate via the socalled Thurau mechanism could also play a role in the development of renal insufficiency in interstitial fibrosis. Structural alterations of the glomeruli seem not to be the cause of interstitial fibrosis – neglecting the focal fibrosis surrounding total hyalinized glomeruli. No correlations could be found in FGS between severity of the glomerular lesions and grade of interstitial fibrosis. In MPI with NS and FGS (Hyman and Burkholder, 1973) the whole nephron seems to be affected; the interrelations between glomerulus and the remaining nephron are not known. Even if in cases of FGS with more affected glomeruli a distinct interstitial fibrosis can be found – rank-correlations are not significant – an influence of these segmental lesions on the postglomerular blood flow may not be proposed. Glomerular structure, consisting of a meshwork of capillaries, leads to a marked enlargement of the surface compared to a sphere of corresponding volume, and thereby to a considerable functional reserve-capacity (Plate, 1976; Eenboom, 1977). Thus it is unlikely that partial destruction of the glomerulus plays a role in glomerular filtration and postglomerular blood flow.

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