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# Impairment of the Glomerular Filtration Rate by Glomerular and Interstitial Factors in Membranoproliferative Glomerulonephritis With Normal Serum Creatinine Concentration

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**Summary**. In different grades of MPGN with normal serum creatinine concentrations a statistical correlation exists between the cortical interstitial volume and the decreasing creatinine clearance. That means that even in the case of a serum creatinine concentration up to 1.2 mg%/100 ml the cortical interstitium may be broadened (up to 30 Vol%) and the creatinine clearance markedly reduced (up to 20 ml/min/1.73 $m^2$) (compare Fischbach et al., 1977).

No significant differences could be established between the means of the serum creatinine concentration, creatinine clearance and relative interstitial volume in the four grades of severity.

Only slight fibrosis in the cortical interstitium leads to an impairment of the GFR. Severe glomerular lesions, however, (grade III and IV) may occur with normal serum creatinine concentration and with normal creatinine clearance provided that the interstitium is not enlarged.

It is conceivable that interstitial fibrosis leads, by a narrowing of the postglomerular vessels, to an elevated effective filtration pressure and to a slowing of glomerular blood flow and reduction of the GFR.

In most cases tubules in fibrotic areas are atrophic – due to ischaemic changes and/or "inactivity". The resorptive capacity of these tubules could be disturbed and the GFR reduced by the so-called "Thurau-Mechanism".

The enormous functional reserve capacity of the glomeruli, however, prevents an impairment of the GFR even in the case of severe glomerular lesions.

**Key words:** Membranoproliferative glomerulonephritis – Normal serum creatinine concentration – Glomerular lesions – Interstitial fibrosis – Impairment of the GFR.

## Introduction

Earlier investigations on different inflammatory and non-inflammatory glomerular diseases showed, that the glomerular filtration rate (GFR) seems to be in-

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fluenced more by the degree of fibrosis of the renal cortical interstitium (relative interstitial volume, RIV) than by glomerular alterations (Bohle et al., 1977a–c; Fischbach et al., 1977). The serum creatinine concentration was used as an indicator of renal function (GFR). The computed curves for the relationship between serum creatinine concentration and RIV showed – (in the range of normal serum creatinine concentration) – that an enlargement of the RIV of up to 20 Vol% was possible while the serum creatinine concentration remained within normal limits. It is also known that in cases of normal serum creatinine concentration (up to 1.3 mg/100 ml) the GFR can be markedly reduced (Haugen et al., 1955). The creatinine clearance ($C_{Cr}$) being a more sensitive parameter of the GFR, was therefore correlated with the RIV of the renal cortex, in the normal range of serum creatinine concentration. Membranoproliferative glomerulonephritis (MPGN) was chosen because the glomerular changes can be divided into different grades of severity (Fischbach et al., 1977) and it is thus possible to assess more accurately the impairment of the GFR by these lesions.

## Materials and Methods

45 renal biopsies from patients with different grades of MPGN were investigated. The biopsy-cylinders, containing more than 5 glomeruli, were fixed in 4% buffered formalin-solution (pH 7.4). 5–8 μ thick paraffine sections, stained with PAS, were measured using the Reichert-Visopan-Projection-Microscope (Objective 40/0.65, magnification 500:1). 5 projection fields per kidney were evaluated under a lattice of 1 cm differentiating between epithelial cells, lumina and interstitium, neglecting glomeruli and large vessels. The severity of the glomerular changes were determined according to the following criteria:

Grade I: Segmental thickening of the glomerular basement membrane and slight mesangial hypercellularity ($n=10$) (Fig. 1a).

Grade II: Diffuse thickening of the basement membrane and more marked mesangial hypercellularity ($n=17$) (Fig. 1b).

Grade III: Glomerular basement membrane diffusely thickened, pronounced mesangial hypercullularity and only slight lobulation ($n=14$) (Fig. 1c).

Grade IV: As grade III, but marked lobulation of the tuft and/or segmental adhesions ($n=4$) (Fig. 1d).

Mean and standard deviation of the following variables for the four grades of severity were computed: serum creatinine concentration, creatinine clearance, relative interstitial volume, systolic and diastolic blood pressure, serum protein concentration, and proteinuria. In addition the mean and standard deviation of the creatinine clearance of the cases with and without the nephrotic syndrome were computed. The frequency of the nephrotic syndrome was also determined. The mean-values of the serum creatinine concentration, endogenous creatinine clearance and of the accompanying relative interstitial volumes of the different grades of severity were compared by the $t$-test. For the relationship between serum creatinine concentration or creatinine clearance and the relative interstitial volume, Spearmans rank correlation coefficient $r_S$ was computed and from the $t$-value the error probability $\alpha$ was determined. Regression equations for the correlation between $c_{Cr}$ resp. serum creatinine concentration and relative interstitial volume for linear, parabolic and exponential functions, the correlation coefficient r and the error probability $\alpha$ were compiled the latter from the $t$-value.

## Results

In the four different grades of MPGN there exist statistically significant correlations between decreasing $C_{Cr}$ and enlargement of the RIV ($r_S = -0.448$, $t=3.2$,

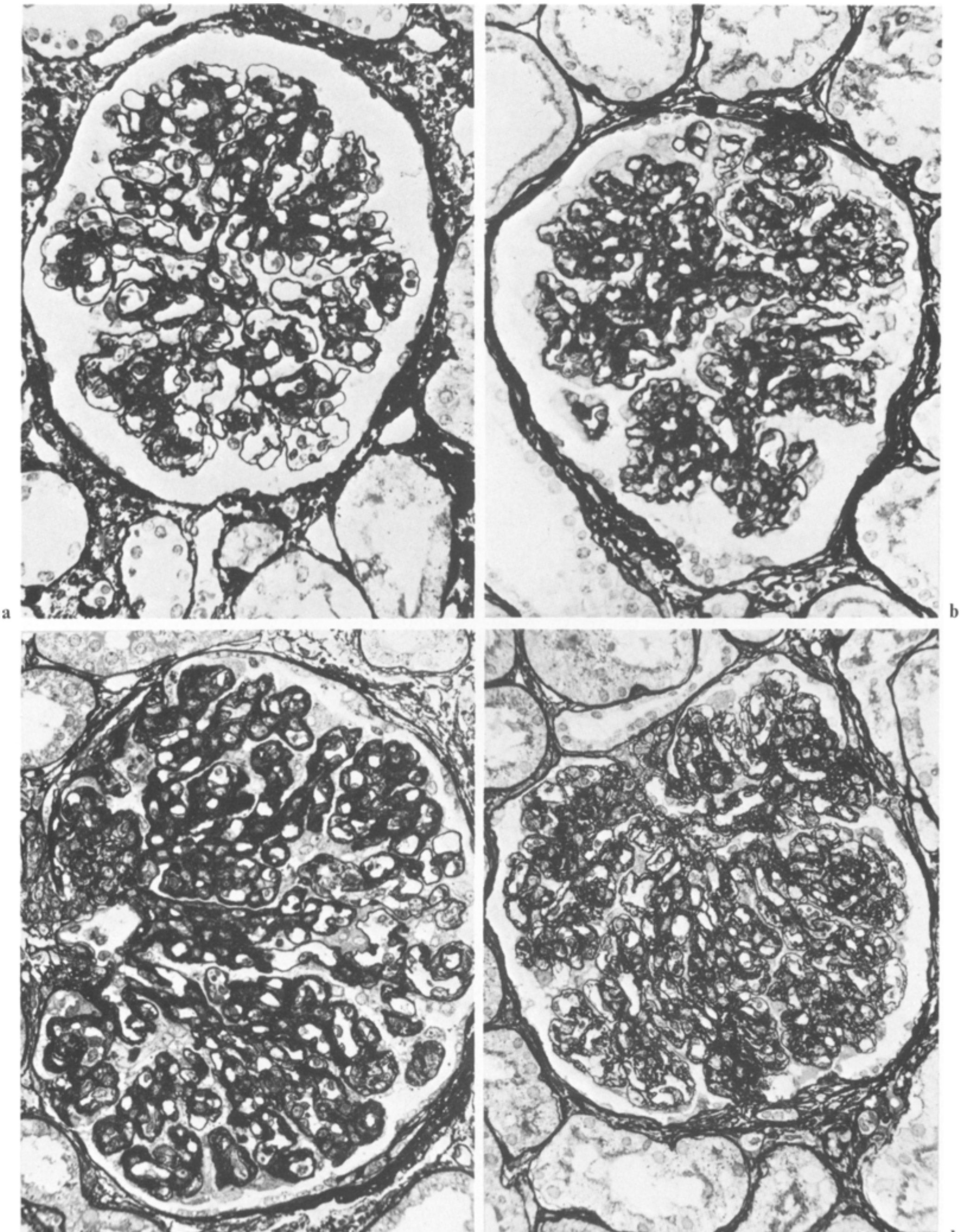

**Fig. 1. a** 7421477, MPGN grade I, serum creatinine concentration 1.2 mg/100 ml, end. creatinine clearance 67 ml/min/1.73 $m^2$. **b** 726280, MPGN grade II, serum creatinine concentration 0.6 mg/100 ml, end. creatinine clearance 150 ml/min/1.73 $m^2$. **c** 764622, MPGN grade III, serum creatinine concentration 1.0 mg/100 ml, end. creatinine clearance 100 ml/min/1.73 $mm^2$. **d** 6931442, MPGN grade IV, serum creatinine concentration 1.0 mg/100 ml, end. creatinine clearance 115.9 ml/min/1.73 $m^2$. **a–d** Semithin-sections, all silver impregnation after Movat, magnification 360:1

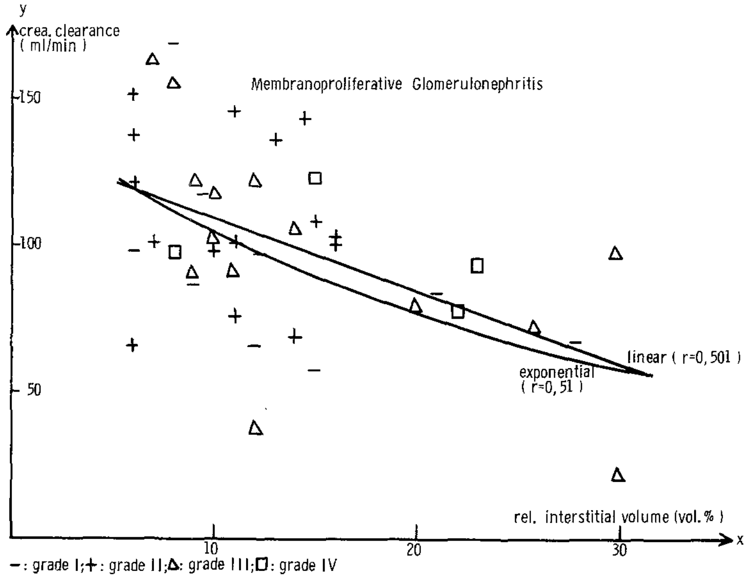


**Fig. 2.** Correlation between endogenous creatinine clearance at the time of biopsy ($y$-axis) and relative interstitial volume ($x$-axis) in the range of normal serum creatinine concentration

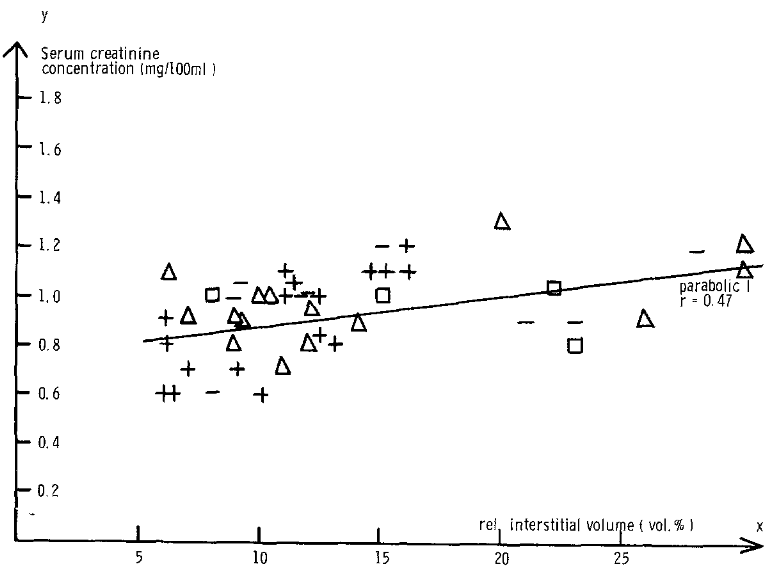


**Fig. 3.** Correlation between serum creatinine concentration at the time of biopsy ($y$-axis) and relative interstitial volume ($x$-axis) in the range of normal serum creatinine concentrations. Same symbols as in Fig. 2

**Table 1.** Analysis of regressions and correlations between relative interstitial volume and $C_{Cr}$ at the time of biopsy in the range of normal serum creatinine concentration

| $x/y$ | Function | Correlation coefficient $r$ | $t$ | Error probability $\alpha$ |
|---|---|---|---|---|
| Linear | $y=132.3-2.43\cdot x$ | 0.501 | 3.6 | $<0.001$ |
| Parab. I | $y=137-3.131\ x+0.020\ x^2$ | 0.502 | 3.674 | $<0.001$ |
| Expon. | $y=140\cdot e^{-0.0305\ x}$ | 0.5108 | 3.758 | $<0.001$ |
| Parab. II | $y=262.7\cdot x^{-0.4150}$ | 0.479 | 3.465 | $<0.002$ |

**Table 2.** Analysis of regressions and correlations between relative insterstitial volume and serum creatinine concentration at the time of biopsy in the range of normal serum creatinine concentration

| $x/y$ | Function | Correlation coefficient $r$ | $t$ | Error probability $\alpha$ |
|---|---|---|---|---|
| Linear | $y=0.758+0.013\ x$ | 0.446 | 3.3 | $<0.005$ |
| Parab. I | $y=0.619+0.033\ x-0.001\ x^2$ | 0.47 | 3.46 | $<0.005$ |
| Exponent. (lin/log) | $y=0.751\cdot e^{0.014}$ | 0.435 | 3.1 | $<0.005$ |
| Parab. II (log/log) | $y=0.528\ x^{0.218}$ | 0.467 | 3.39 | $<0.005$ |

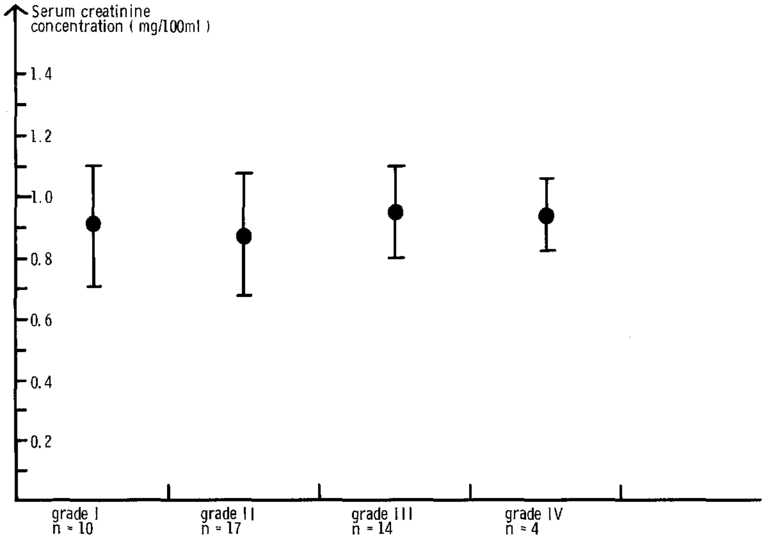


**Fig. 4.** Statistical analysis: Grade of MPGN and mean serum creatinine concentration at the time of biopsy. No significant differences between all groups

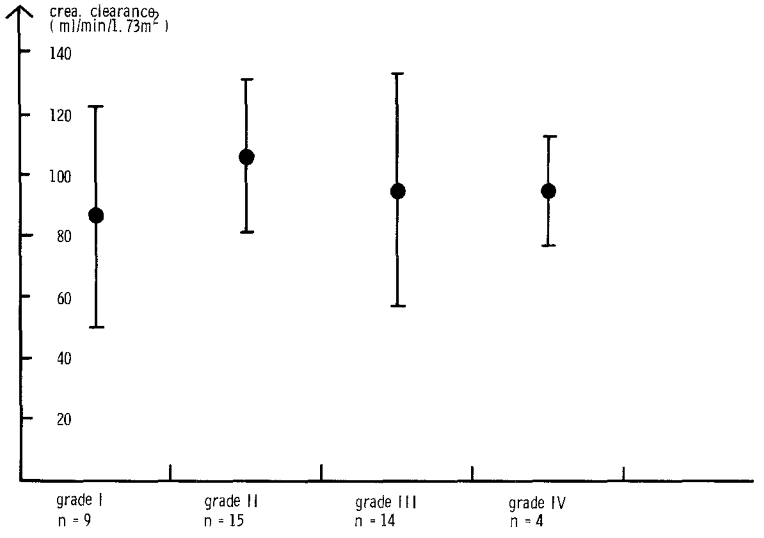


**Fig. 5.** Statistical analysis: Grade of MPGN and mean $C_{Cr}$ at the time of biopsy. No significant differences between all groups

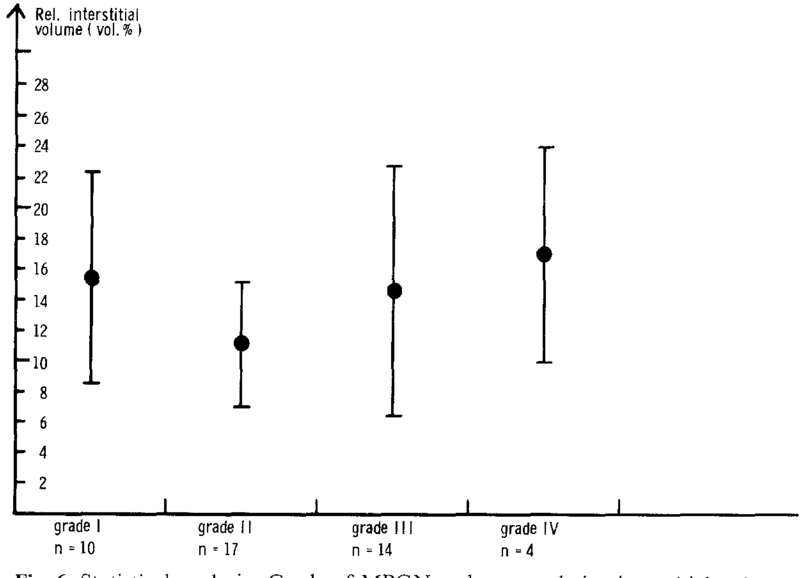


**Fig. 6.** Statistical analysis: Grade of MPGN and mean relative interstitial volume. No significant differences between all groups

**Table 3.** Morphological parameters and clinical data in the four grades of severity

| | Grade I | Grade II | Grade III | Grade IV |
|---|---|---|---|---|
| $n=45$ | 10 | 17 | 14 | 4 |
| Creatinine concentration (mg/100 ml) | $0.955 \pm 0.21$ | $0.88 \pm 0.21$ | $0.952 \pm 0.16$ | $0.96 \pm 0.10$ |
| $C_{Cr}$ (ml/min/1.73 m$^2$) | $92.66 \pm 33.41$ $n=9$ | $109.26 \pm 27.65$ $n=15$ | $95.92 \pm 38.58$ $n=14$ | $95.50 \pm 18.73$ $n=4$ |
| Relative interstitial volume (Vol%) | $14.465 \pm 7.29$ | $11.147 \pm 4.037$ | $14.857 \pm 8.16$ | $17.0 \pm 9.976$ |
| $p$ systol. (mm Hg) | $149.5 \pm 21.14$ $n=10$ | $150.29 \pm 36.84$ $n=17$ | $155.83 \pm 34.43$ $n=12$ | $167.5 \pm 28.72$ $n=4$ |
| $p$ diast. (mm Hg) | $90 \pm 13.3$ $n=10$ | $92.058 \pm 18.2$ $n=17$ | $92.5 \pm 17.1$ $n=12$ | $88.75 \pm 10.3$ $n=4$ |
| Total serum protein (g/100 ml) | $6.63 \pm 0.64$ $n=9$ | $5.85 \pm 1.2$ $n=17$ | $5.88 \pm 1.34$ $n=11$ | $5.6 \pm 0.75$ $n=3$ |
| Proteinuria (g/die) | $3.02 \pm 3.98$ $n=9$ | $3.74 \pm 3.09$ $n=17$ | $4.90 \pm 2.68$ $n=12$ | $5.6 \pm 5.5$ $n=3$ |
| Means of $C_{Cr}$ (cases with the nephrotic syndr.) | $125.0 \pm 59.39$ $n=2$ | $122.50 \pm 32.72$ $n=6$ | $106.4 \pm 34.731$ $n=5$ | 75 $n=1$ |
| Means of $C_{Cr}$ (cases without nephr. syndr.) | $86.16 \pm 21.92$ $n=6$ | $100.4 \pm 21.21$ $n=9$ | $99.3 \pm 44.243$ $n=6$ | $93.5 \pm 4.95$ $n=2$ |
| With NS/without NS | 2/7 | 7/10 | 5/6 | 1/2 |
| Mean of age | $29.2 \pm 14.9$ | $30.05 \pm 11.49$ | $28.42 \pm 17.5$ | $25.25 \pm 12.2$ |
| ♂:♀ | 4:6 | 6:10 | 8:5 | 2:2 |

No significances between groups

$\alpha < 0.005$). The computed curves are best represented by exponential and parabolic functions (see Fig. 2, Table 1). Statistically significant positive correlation also exist between serum creatinine concentration and relative interstitial volume in the range of normal serum creatinine concentration. The correlation, however, is less close (Fig. 3, Table 2).

There are no significant differences between the means of the serum creatinine concentration, $C_{Cr}$ and RIV in the four different grades of severity (Figs. 4, 5, 6). The most important clinical data of the 45 investigated cases can be seen in Table 3.

## Discussion

In all four grades of severity of MPGN the serum creatinine concentration and $C_{Cr}$ may be found to be normal provided that the RIV is not enlarged by fibrosis. In the range of normal serum creatinine concentration the relative interstitial volume correlates with the decreasing $C_{Cr}$, which means that even

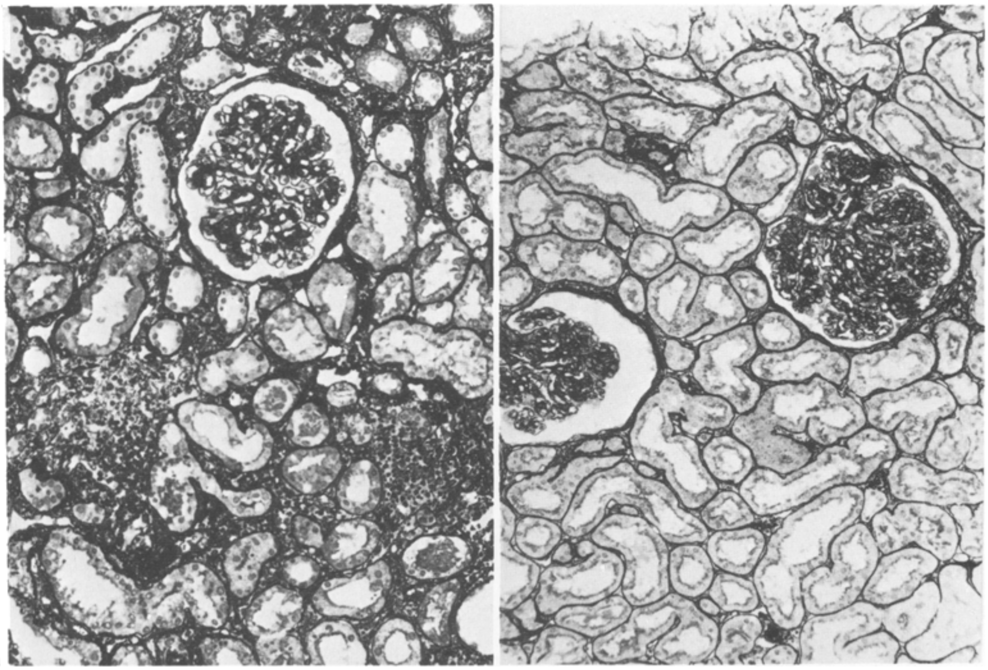

**Fig. 7. a** 7421477, MPGN grade I. With little interstitial fibrosis. Serum creatinine concentration 1.2 mg/100 ml, end. creatinine clearance 67 ml/min/1.73 $m^2$. **b** 6931442, MPGN grade IV. Normal looking surrounding tubules, not enlarged interstitium. Serum creatinine concentration 1.0 mg/100 ml, end. creatinine clearance 115,9 ml/min/1.73 $m^2$

a slight increase in the RIV impaires the GFR significantly. This additional correlation was not observed in the former paper of Fischbach et al., 1977.

These results confirm the findings of former investigations, which have shown that the GFR seems to be influenced mainly by the postglomerular vessel network (Bohle et al., 1977a–c; Fischbach et al., 1977; Mackensen et al., 1977; 1978, Grund et al., 1978). We have also concluded that the enormous functional reserve capacity which exists in the glomeruli means that even severe structural lesion, which are found regularly in grade III and IV of MPGN in all glomeruli (Fig. 1c, d) do not lead to a measurable reduction of the GFR (using $C_{Cr}$).

It is therefore not surprising that minimal glomerular lesions – as in minimal change disease – (Bohle et al., 1977c) where a reduction of the capillary surface of the glomeruli does not certainly occur may be accompanied by elevated serum creatinine concentrations when the cortical interstitium is broadened by fibrosis. In contrast cases of severe glomerular disease, which may lead to a distinct reduction of the surface of the capillaries by swelling and proliferation of cells (endothelial- and mesangial cells), may have normal $C_{Cr}$, provided that the postglomerular vessel network is intact (Fig. 7a, b).

A reduction of the glomerular bloodflow is conceivable if the postglomerular vessel network is narrowed by scarring in the interstitium. Collagen fibres appear to be increased in a broadened interstitium. This narrowing leads to a rise of the postglomerular flow resistance and thereby to an elevation of the effective intraglomerular filtration pressure. Initially this elevated pressure in the glomerular capillaries keeps the GFR constant in spite of the reduction of the cortical blood flow. Later the further decrease in cortical blood flow, however, leads to a reduction of the GFR with a consequent rise of the serum creatinine concentration.

In most cases of interstitial fibrosis the tubules are atrophied although whether by disuse or malnutrition is uncertain. The resorptive capacity of these atrophied tubules may be diminished, so impairing the glomerulumfiltrate by the so-called Thurau-mechanism.

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