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Serum Creatinine Concentration and Renal Interstitial Volume

Analysis of Correlations in Endocapillary (Acute) Glomerulonephritis and in Moderately Severe Mesangioproliferative Glomerulonephritis

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Summary. Renal biopsies of 44 patients with endocapillary acute glomerulonephritis (gn) and 64 patients with moderately severe mesangioproliferative gn were investigated morphometrically (point-counting-method, tubulometry).

In both gn's statistically significant positive correlations between relative interstitial volume and the concentration of serum creatinine at the time of biopsy were found.

Despite severe glomerular lesions the serum creatinine concentration is not increased in most cases of endocapillary acute gn, providing the relative interstitial volume is not increased by more than 15%.

Increased serum creatinine concentration without a markedly enlarged interstitium was found in 11 cases of endocapillary acute gn with clinically and morphologically proven acute renal failure. In these cases the glomerular function is probably impaired by the Thurau-mechanism.

In all other patients, especially in those with moderately severe mesangioproliferative gn, the serum creatinine concentration rises with an enlargement of relative interstitial volume. This reduction of renal function may be explained by a decrease to the total cross-sectional area of postglomerular vessels, caused by interstitial fibrosis. That may possibly lead to diminished renal blood flow and glomerular filtration with an increase of the serum creatinine concentration.

Key words: Endocapillary (acute) glomerulonephritis – Moderately severe mesangioproliferative glomerulonephritis – Glomerular lesions – Interstitial fibrous – Renal insufficiency.

Introduction

In peri- (extra- or epi-) membranous glomerulonephritis (gn) (stages I–III Ehrenreich and Churg, 1968) and in membranoproliferative gn with glomerular lesions

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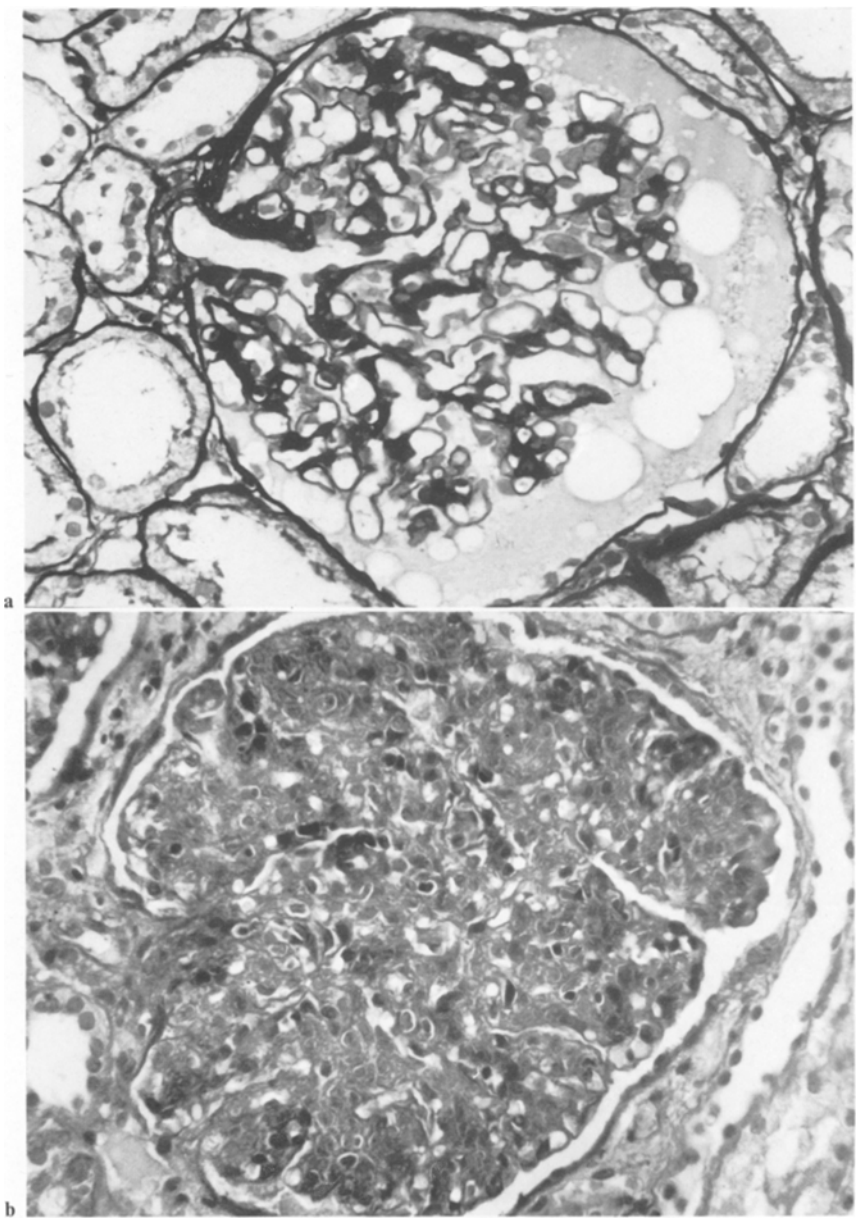

Fig. 1 a and b. All glomeruli PAS-reaction, 360 : 1. **a** Normal kidney (76121622) (ser. crea. 1.2 mg/100 ml). **b** Endocapillary (acute) gn (7411172) (ser. crea. 1.4 mg/100 ml)

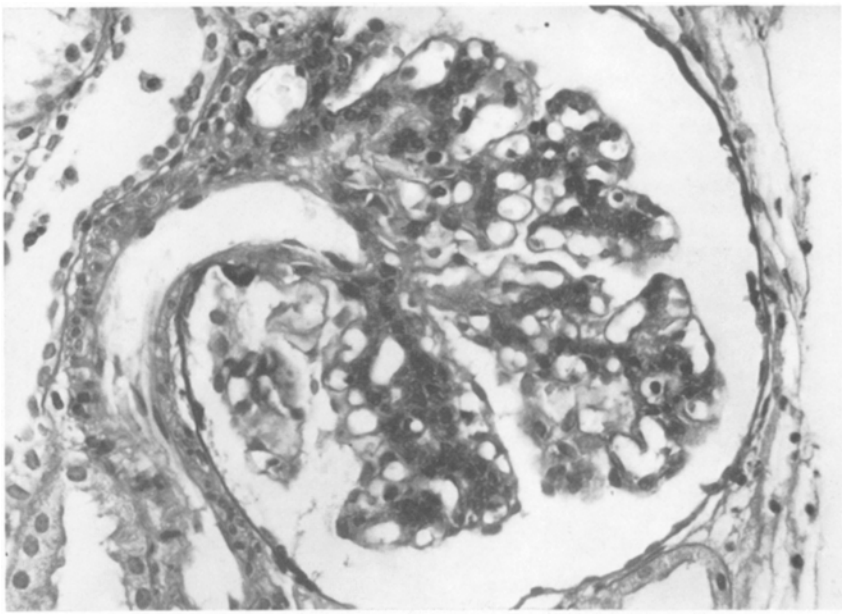

Fig. 1c. Moderately severe mesangioproliferative gn (ser. crea. 0,7 mg/100 ml) (723346)

of different grades, statistically significant correlations between the enlargement of the renal interstitium and the serum creatinine concentration were shown (Bohle et al., 1977; Fischbach et al., 1977). The purpose of our present paper is to determine whether and to what extent similar relationships exist in endocapillary (acute) gn (post-streptococcal type) and in moderately severe mesangioproliferative gn.

In endocapillary (acute) gn (Synonyms: Diffuse proliferative endocapillary gn or endocapillary gn (Habib, 1970, 1972); exsudative and proliferative gn (Cameron, 1970); mixed exsudative and proliferative gn (Thoenes, 1973); diffuse proliferative and exsudative gn (Kincaid-Smith and Hobbs, 1972)) the glomeruli differ from the normal primarily in a notable increase and swelling of mesangium- and endothelial cells and in the appearance of numerous granulocytes in the glomerular tuft (Fig. 1b). The capillary lumina are almost obliterated, in particular endothelial cells are not infrequently detached from the basement membrane by subendothelial oedema (Bohle et al., 1976; Bohle, 1976).

In mesangioproliferative gn we investigated the form which, in respect of the glomerular lesions, could be classified as moderately severe (Fig. 1c) (Bohle, 1976; Bohle et al., 1976). In this disease the cells in the mesangial position – some of them are endothelial cells (Helmchen et al., 1977) – are obviously increased in number compared to normal. The basement membranes of the glomerular capillaries are smooth, the capillary lumina mostly wide open.

Mesangioproliferative gn can develop during the healing period of endocapillary acute gn. Usually however it begins idiopathically.

Materials and Methods

44 endocapillary acute gn's and 64 mesangioproliferative gn's were examined in 5 μm thick PAS- or Goldner trichrome stained paraffin sections. Fixation was performed in 4% formalin pH 7.4. The tissue specimens – mainly biopsy cylinders – contained at least 10 glomeruli.

Sections were investigated 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 neglecting glomeruli and large vessels. The obtained values – relative interstitial volumes (relative to the renal cortex) – were correlated with the concentration of serum creatinine 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. Furthermore, in endocapillary gn with acute renal failure (a.r.f.), cross-sections of 20 proximal tubules per kidney were investigated by planimetry (microscope with drawing tubus (objective 40/0.65), projection on measuring board (MOP AM 01 Kontron Ltd. Munich)). The measured values of the different areas were analysed statistically and compared with 20 normal kidneys.

Results

Relative interstitial volume and corresponding serum creatinine concentration are plotted for the cases of endocapillary gn without a.r.f. in Figure 2.

The results of the correlation – and regression analysis are shown in Table 1.

The values for endocapillary (acute) gn with acute renal failure can be seen in Figure 3 and the results of tubulometry in Table 2.

In most cases of endocapillary gn (duration of illness 1–12 weeks) creatinine concentrations do not exceed 2 mg/100 ml with relative interstitial volumes up to 15%, in spite of the most marked glomerular lesions. In the few cases of this disease with creatinine concentrations over 2 mg/100 ml the interstitium is enlarged.

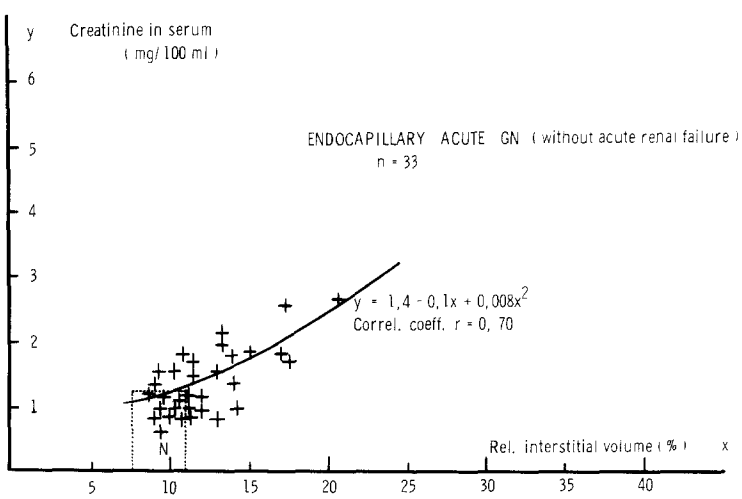

Fig. 2. Correlation between relative interstitial volume (x-axis) and serum creatinine concentration (y-axis) at the time of biopsy. (*N* Range of normal kidneys)

Table 1. Analysis of regressions and correlations between relative interstitial volume and serum creatinine at the time of biopsy in endocapillary acute gn *without* acute renal failure

x/y	Function	Correl. coeff. r	Error prob. α
linear (lin/lin)	$y = -0.018 + 0.12x$	0.68	<0.0001
parabolic I	$y = 1.406 - 0.1x + 0.008x^2$	0.70	<0.0001
exponential (lin/log)	$y = 0.523 \cdot e^{0.077x}$	0.61	<0.001
parabolic II (power) (log/log)	$y = 0.132 \cdot x^{0.934}$	0.58	<0.001

Means: Interstitium (x): 12.5 ± 2.99 Vol%. Creatinine (y): 1.41 ± 0.51 mg/100 ml. Age of patients: 31.4 ± 17 years

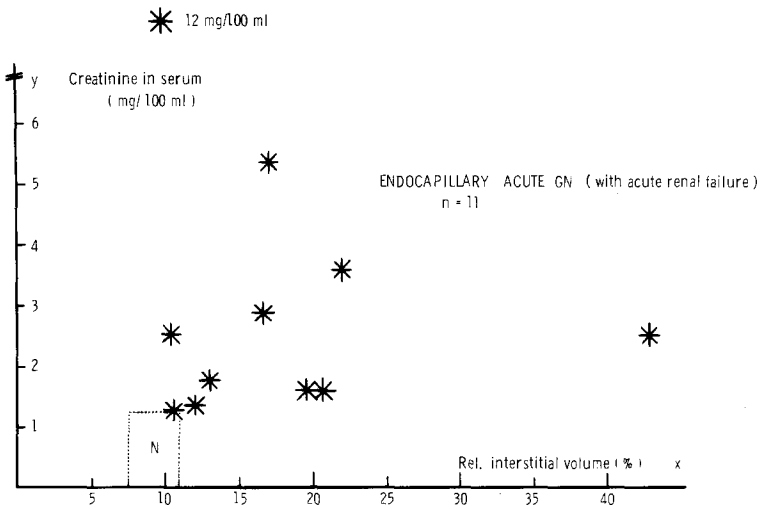

Fig. 3. Correlation between relative interstitial volume (x-axis) and serum creatinine concentration (*N* Range of normal kidneys)

Table 2. Results of tubulometry in endocapillary acute gn with additional acute renal failure. The differences are highly significant

	Controls Normal kidneys $n=20$	Endocap. ac. gn wth a.r.f. $n=11$	*t*-Test	
			t	2p
Total tubular area	$284 \pm 36\,\mu m^2$	$387 \pm 46\,\mu m^2$	5.32	<0.0001
Luminal area	$121 \pm 22\,\mu m^2$	$176 \pm 47\,\mu m^2$	3.23	<0.01
Epithelial area	$153 \pm 21\,\mu m^2$	$211 \pm 25\,\mu m^2$	5.08	<0.001

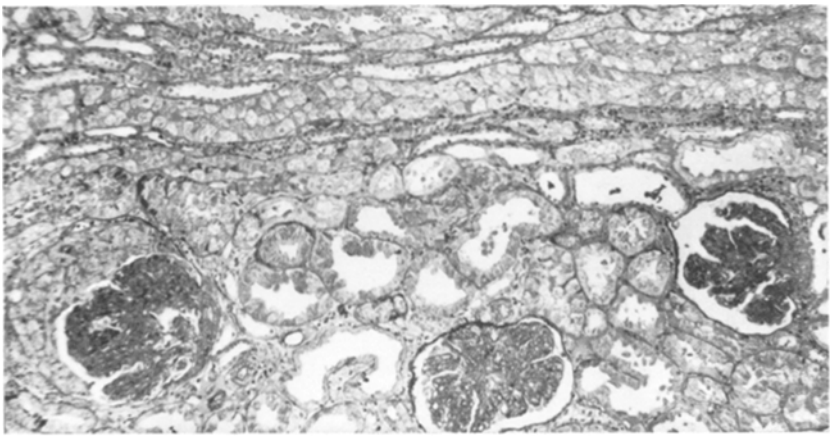

Fig. 4. Detail of the renal cortex in endocapillary acute gn with acute renal failure (7410576). Ser. creatinine 12.6 mg/100 ml. Swelling of the tubular epithelial cells, desquamation of some epithelial cell tops into the lumina of the tubules. Goldner-trichrome, 90:1. This case is not plotted in Figure 2

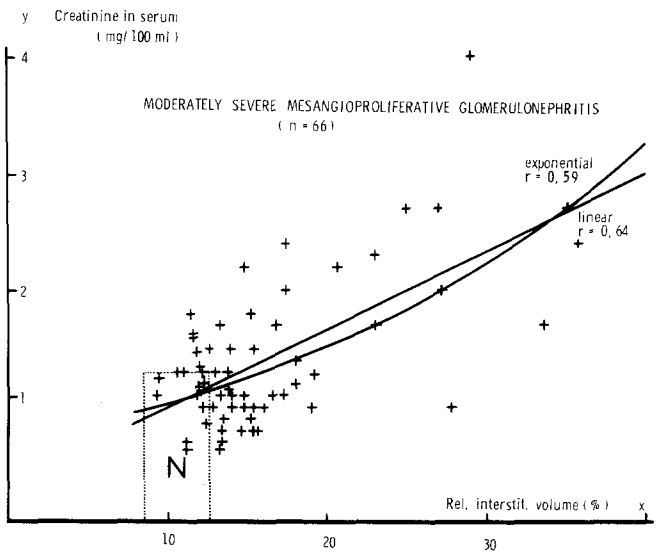

Fig. 5. Correlation between relative interstitial volume (x-axis) and serum creatinine concentration (y-axis) at the time of biopsy. (*N* Range of normal kidneys)

No relationship (rank correlations, $r_s = 0.46$, $t = 1.50$, $\alpha > 0.1$) between relative interstitial volume and serum creatinine concentration can be found in cases of endocapillary acute gn with clinically and morphologically verified acute renal failure (Figs. 3 and 4, Table 2).

Values for moderately severe mesangioproliferative gn can be seen in Figure 5 and Table 3.

Table 3. Analysis of regressions and correlations between relative interstitial volume and serum creatinine at the time of biopsy in moderately severe mesangioproliferative gn

x/y	Function	Correl. Coeff. r	Error probab. α	t
linear (lin/lin)	$y=0.330+0.066x$	0.64		6.679
parabolic I	$y=0.246+0.075x-0{,}0002x^2$	0.641	<0.0001	6.683
exponential (lin/log)	$y=0.695\ e^{0.038x}$	0.59		5.851
parabolic II (log/log)	$y=0.180\ x^{0,721}$	0.575		5.620

Means: Interstitium (x): 16.38 ± 36.6 Vol%. Creatinine (y): 1.41 ± 0.38 mg/100 ml. Age of patients: 31.4 ± 17 years

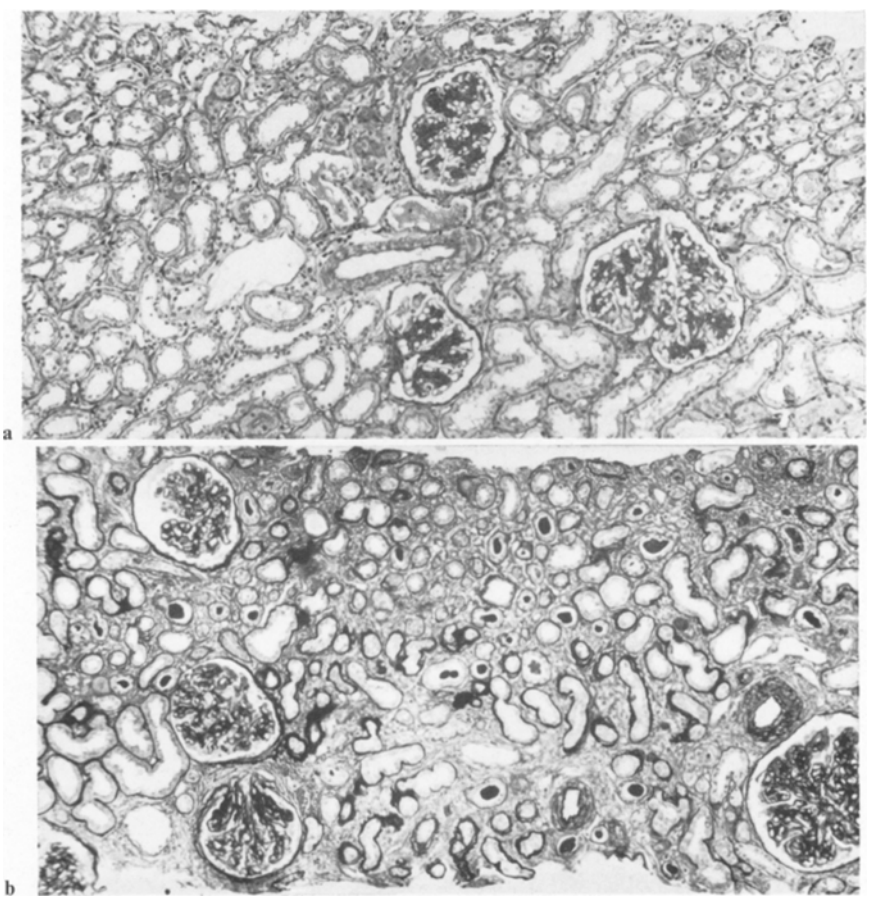

Fig. 6. a Renal cortex of moderately severe mesangioproliferative gn. Normal tubules and interstitium. Ser. crea. 1.0 mg/100 ml (7111615). **b** Moderately severe mesangioproliferative gn. Atrophy of the tubules and nearly diffuse interstitial fibrosis. Ser. crea. 3.1 mg/100 ml (7612955). PAS-reaction, 90:1

In all cases of moderately severe mesangioproliferative gn, in contrast to the cases of endocapillary acute gn with acute renal failure, there were relationships between the relative interstitial volume and the serum creatinine concentration (Fig. 3, Table 3, Fig. 5). The values are best represented by parabolic and linear functions.

Discussion

In attempting to correlate structure and function in glomerulonephritis, Parrish et al. (1961, 1962) have observed in the acute form and Brod et al. (1957) in the chronic, relationships between the severity of glomerular lesions and reduction of the glomerular filtration rate. Risdon et al. (1968) and De Wardener (1973) however, found in their investigations based on renal biopsy material of 50 patients with various, mainly glomerular renal diseases, no correlations between the severity of the glomerular lesions and deterioration of renal function measured by reduction of creatinine-clearance, plasma-creatinine and ability to concentrate urine.

At first glance our observations seem to correspond with the latter results. If one critically examines the interpretation of these findings however, the lack of correlation between the severity of the glomerular lesions and functional deterioration measured by creatinine-clearance, plasma creatinine-concentration and the ability of the kidney to concentrate and acidify the urine is explained by an obstruction- and back-diffusion theory: the glomerular filtration rate could, in the case of minimal glomerular damage, be falsified by the presence of blocking casts in the tubules, or by a non-selective back-diffusion of the ultrafiltrate due to "leaks" in the tubular basement membrane.

Arguments have previously been developed against a blockade- and back-diffusion theory as explanation for the reduced glomerular filtration rate without glomerular involvement (Bohle, 1964; Bohle, 1967; Bohle et al., 1976). We occasionally found casts of erythrocytes, hemoglobin and protein independent of the serum creatinine level, more richly in endocapillary glomerulonephritis than in the mesangioproliferative glomerulonephritis. With regard to the importance of the interstitium for renal function, relationships – partly in form of rank correlations – between alterations of the interstitium and a reduction of the clearance were shown by Muerhcke et al. (1957), Risdon et al. (1968), De Wardener (1973) as well as by Schainuck et al. (1970). The "ominous importance" of the interstitium for prognosis of renal alterations found in generalized Lupus erythematodes has been emphasized by Muerhcke et al. (1957). According to Dunnill et al. (1975) the prognosis of so called segmental gn's – a heterogenous group of glomerular diseases – is worse when an enlarged interstitium is found.

In support of these findings, in 4 different themselves homogenous, well defined gn's (perimembranous, membranoproliferative, moderately severe mesangioproliferative and endocapillary (acute) gn) relationships in form of regression equations could be established between serum creatinine concentration and relative interstitial volume (Bohle et al., 1977; Fischbach et al., 1977).

The curve for endocapillary acute gn without a.r.f. (Fig. 2) shows that even in severe inflammatory glomerular lesions, no elevation of serum creatinine concentration are found provided that the renal interstitium is not enlarged.

This might be explained by the fact that, according to the experiments of Brenner et al. (1976), less than the whole capillary surface is required for the filtration process, under normal conditions. Glomerular structure, consisting of a meshwork of capillaries, results in an extreme enlargement of the surface (680-times) compared to a sphere of corresponding volume, and thus provides a considerable functional reserve-capacity (Plate, 1976).

In cases of moderately severe mesangioproliferative gn, in which the glomeruli appear much less damaged than in endocapillary acute gn, increased serum creatinine values are found. These are almost invariably combined with an enlarged renal interstitium.

Where there are no correlations between the serum creatinine concentration and the volume of the renal interstitium—as in 11 cases of endocapillary acute gn—epithelial swelling of the proximal tubules, demonstrated by morphometry, further epithelial cell necrosis, regenerating epithelial cells and mitoses are found, changes typical of acute renal failure (Bohle, 1967; Bohle et al., 1976). Defective NaCl-resorption caused by these damages can lead by the Thurau-mechanism (Thurau and Schnermann, 1965) to a reduction of the GFR and thus to an increase of the serum creatinine level (Bohle and Thurau, 1974; Thurau and Boylan, 1976).

In the collected cases in which acute renal failure could be excluded, there exist, however, statistically established correlations between the serum creatinine concentration and the relative interstitial volume.

It may be that these correlations are merely formal and the enlargement of the renal interstitium may be a complementary phenomenon in an unknown disturbance of renal function. We think it to be more probable that the enlargement of the interstitium, mainly resulting from fibrosis, is the cause of the decrease of the glomerular filtration rate. As a hypothesis we suggest that the enlargement by fibrosis of the interstitium may lead to a decrease of the cross-sectional area of the postglomerular vessel network. This process could impair glomerular function, so that even in the case of minimal, or indeed in the absence of visible changes in the glomeruli the serum creatinine increases.

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