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Review

IgA-Nephropathy (IgA-IgG-Nephropathy/IgA-Nephritis) – a Disease Entity?

A Comparative Analysis of Immunohistologic, Histologic and Clinical Findings in 166 Renal Biopsies of 153 Patients

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Summary. From 166 renal biopsies of 153 patients who showed the dominating mesangial IgA deposits of "IgA-Nephropathy", relationships were established between immunohistologic, histologic and clinical findings with the following results:

1. The immunohistologic picture of IgA-Nephropathy exhibits a broad histologic spectrum including cases with histologically normal findings as well as mesangioproliferative Gn with focal and diffuse crescents. Most often the morphologic changes are associated with a mild and moderately severe mesangioproliferative Gn.

2. According to the extent of the morphologic lesions no discrepancy between immunohistologic and histologic findings exists. Excluding a few cases with a focal accentuation of the histologic picture the histologic lesions as well as the immunofluorescence pattern are diffuse.

3. The immunohistologic picture of IgA-Nephropathy cannot be associated with uniform and characteristic clinical and morphologic pictures. Therefore, the predominant mesangial IgA deposits of the IgA-Nephropathy-type should not be regarded as a clinical – morphologic entity but rather as a specific immunohistologic symptom with possible different underlying pathomechanisms, probably controlled by a common genetically determined aberrant immune response with in consequence various morphologic reactions of different intensity and with a relatively favorable prognosis in most cases.

Key words: IgA-Nephropathy – Focal glomerulonephritis – Mesangioproliferative glomerulonephritis – Mesangium – Hematuria – Immunohistology.

Introduction

Based on the distinct immunohistologic pattern dominated by IgA- and generally additional IgG- and C_3-deposits in the mesangium, IgA-IgG-Nephropathy was

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defined by Berger and Hinglais (1968) as a form of glomerulonephritis manifested clinically by a recurring macrohematuria, or microhematuria and proteinuria and histologically as a focal glomerulonephritis. Meanwhile further glomerular lesions in addition to a focal proliferative glomerulonephritis have been described by other authors (Druet et al., 1970; Morel-Maroger et al., 1972; Levy et al., 1973; De Werra et al., 1973; Mc Coy et al., 1974; Sissons et al., 1975; Shirai et al., 1978; Yokoska et al., 1978) i.e. minimal changes, diffuse mesangioproliferative glomerulonephritis, mesangioproliferative glomerulonephritis with focal or diffuse crescents.

These observations along with the discrepancy between a diffuse immunohistologic picture affecting the entire glomerulus and alleged predominately focal histologic changes prompted us to compare the immunohistologic findings with the morphologic changes and the clinical picture of IgA-Nephropathy in our biopsy material. In doing so, we hoped to answer the question if and what type of relationships exist between the immunohistologic, histologic and clinical picture in IgA-Nephropathy and whether a distinction of IgA-Nephropathy as a disease entity is justified from the clinical-morphologic aspect.

Materials and Methods

166 renal biopsies were evaluated histologically and immunohistologically from 153 patients with IgA-Nephropathy diagnosed on the basis of immunohistologic findings. 13 patients were rebiopsied after an average of 1 year. The immunohistologic studies were performed on 3–4 μ cryostat-sections from renal biopsies or wedge excisions which had been incubated according to the method of Coons and Kaplan (1950) for 30 min at room temperature in a moist chamber with FITC labeled human antisera to IgG, IgM, IgA, IgD, IgE, C1q, C4, C3, fibrinogen, HAA and albumin (Behring-Werke Marburg). The antisera fulfilled the following specifity criteria: 1. Protein concentration of the gamma-globulin fraction conjugated with FITC: 10 ± 3 mg/ml. 2. Total protein concentration (upon addition of human albumin): 40 ± 5 mg/ml. 3. Specific antibody fraction: $10 \pm 5\%$ of the gamma-globulin concentration $= 2.5 \pm 1.5$. 4. Molar SP (serum protein)-quotient: 2.0–3.2. The antibody specificity was determined by immunoprecipitation. The lyophilized sera were dissolved in distilled water and diluted 1:8 with PBS (pH 7.2). Following a 30 min incubation period the slices were washed $3 \times 10'$ with PBS (pH 7.2) and finally mounted with PBS-glycerin. As controls the direct method with albumin was used and in some cases the indirect method (Coons and Kaplan, 1950). The immunohistologic investigations were carried out on a Zeiss fluorescence microscope with incident illumination. Cases with systemic diseases (Schönlein-Henoch-Syndrom, Alport-Syndrom, systemic lupus erythematosus) were eliminated in the present study. The light microscopic examinations were performed on PAS-stained sections, embedded in paraffin, and partly on silver-stained semi-thin sections (1 μ), embedded in plexiglass. In addition, 23 cases were examined electron-microscopically. Since not only correlations between immunohistology and histology but also between structure and function were to be investigated in our study, the following clinical findings and laboratory data along with age and sex were included in our evaluation: 1. Previous diseases, 2. initial symptoms of the disease, 3. duration of the disease (period between the first renal symptom and renal biopsy), 4. blood pressure: RR systolic/diastolic (mm Hg) (a systolic value more than 160 mm Hg and a diastolic value more than 95 mm Hg was considered to be elevated), 5. frequency of the nephrotic syndrome (definition of nephrotic syndrome: proteinuria more than 3 g/die, total protein concentration less than 6 g/100 ml, albuminemia below 3 g/100 ml = 50 rel.%), 6. proteinuria (g/die)), 7. leukocyturia, 8. hematuria (severity classified as follows: a) negative, b) + = 3–10 per field of vision = 3–6,000/min, c) + + = 11–20 per field of vision = 6–10,000/min, d) + + + and macrohematuria = more than 20 erythrocytes per field of vision = more than 10,000 ery/min, 9. serum creatinine (mg%), 10. creatinine clearance (ml/min per 1.73 m^2) (creatinine-clearance values less than 80 ml/min/1.73 m^2 were regarded as being mildly restricted and less than 40 ml/min/1.73 m^2 as markedly restricted), 11. AST-, Complement-, Immunglobulin-levels in serum.

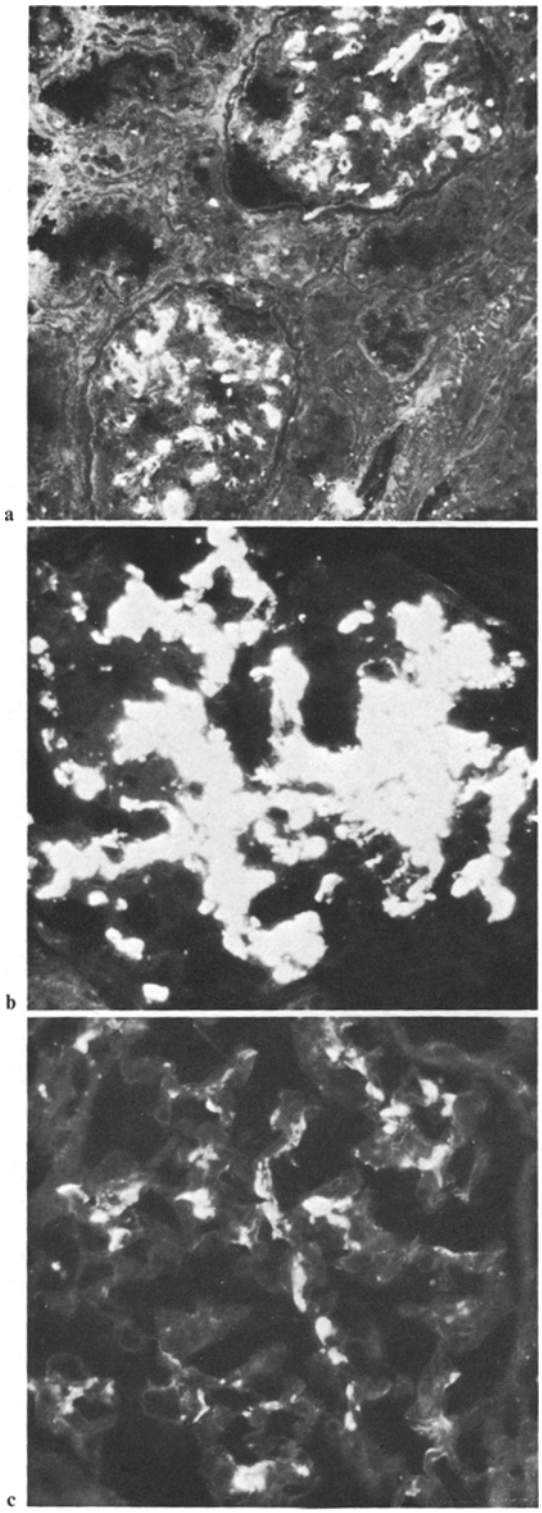


Fig. 1. a "IgA-Nephropathy". Mesangial arborescent fluorescence pattern, IgA, 128:1
b "IgA-Nephropathy". Moderately severe mesangioproliferative glomerulonephritis with intensive mesangial fluorescence pattern. IgA, 400:1
c "IgA-Nephropathy". Mild mesangioproliferative glomerulonephritis with less mesangial fluorescence compared to Fig. 1b. IgA, 640:1

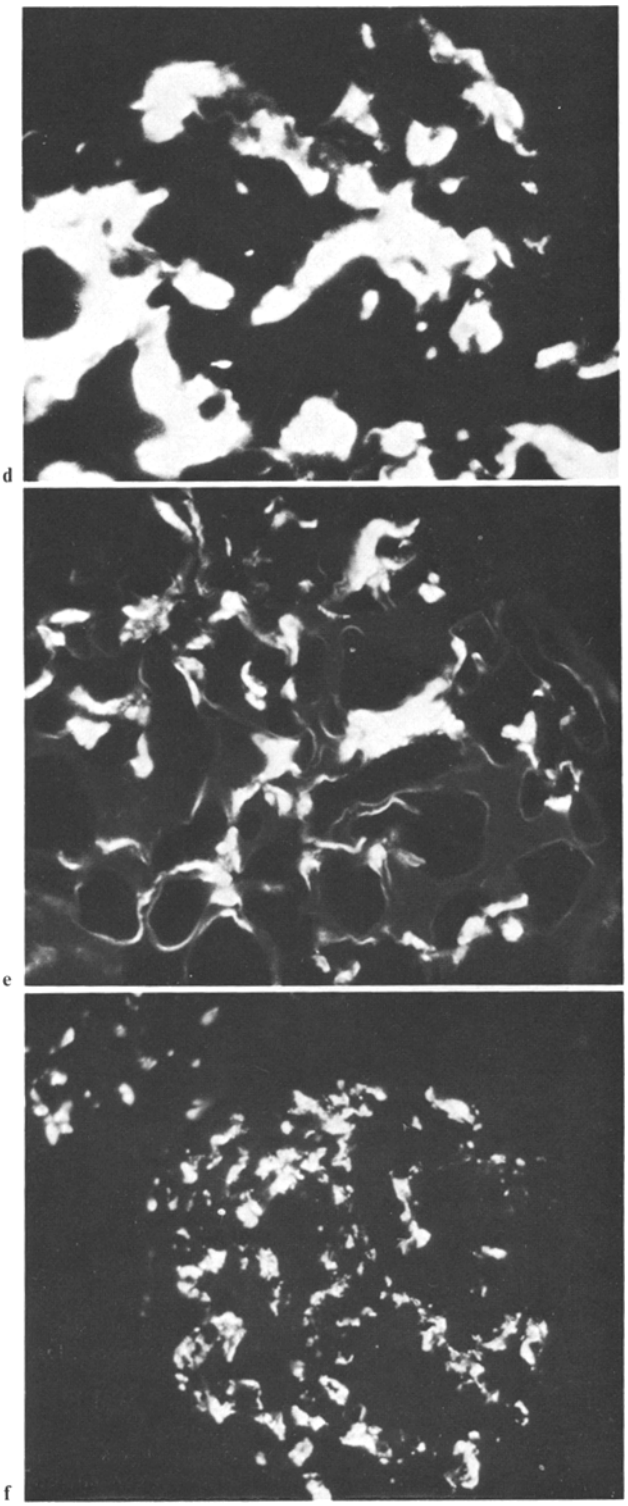


Fig. 1. d "IgA-Nephropathy". Mild mesangioproliferative glomerulonephritis with fluorescence appearing homogenously. IgA, 640:1
e "IgA-Nephropathy". Mild mesangioproliferative glomerulonephritis with striped, doubly contoured fluorescence pattern. IgA, 640:1
f "IgA-Nephropathy". Mild mesangioproliferative glomerulonephritis with coarsely granular fluorescence pattern. IgA, 400:1

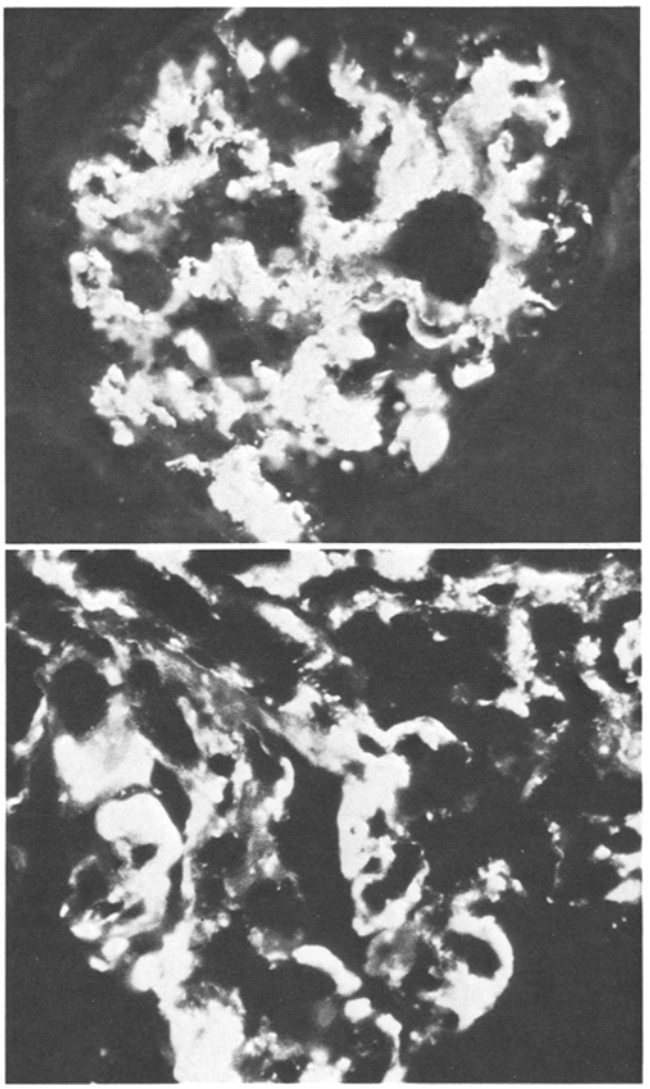


Fig. 1. g "IgA-Nephropathy". Moderately severe mesangioproliferative glomerulonephritis with lumpy fluorescence pattern. IgA, 400:1
h "IgA-Nephropathy". Severe mesangioproliferative glomerulonephritis – mesangial fluorescence, extending into adjacent glomerular loops. IgA, 640:1

Results

1. Morphologic Findings

1. Immunohistology

All cases show a mesangial arborescent fluorescence pattern (Fig. 1a) with IgA deposits of varying intensities (Fig. 1b and c) and a character which is

Table 1. Immunohistological findings in 166 renal biopsies of IgA-Nephropathy: Nature and frequency of deposits

$n=166$	IgA	IgG	IgM	IgE	C_3
	166/166	76/166	52/166	4/166	158/166

One or several immunoglobulins isolated			One immunoglobulin combined with C_3	Several immunoglobulins combined with C_3			
5%			41%	54%			
IgA	IgA+IgG	IgA+IgM	IgA+C_3	IgA-IgG +C_3	IgA+IgG +IgM+C_3	IgA+IgM +C_3	IgA+IgE +C_3
3.8%	0.6%	0.6%	41%	20%	24.8%	6.8%	2.4%

Table 2. Histologic findings in 166 renal biopsies of IgA-Nephropathy

Type of glomerulonephritis (Gn) $n=166$:

Normal	Minimal proliferating intercapillary Gn	Mesangioproliferative Gn			Mesangioproliferative Gn with crescents		Focal sclerosing GN
		mild	moderately severe	severe	focal	diffuse	
$n=3$	$n=31$	$n=66$	$n=50$	$n=8$	$n=5$	$n=2$	$n=1$
2%	18%	40%	30%	5%	3%	1.3%	0.7%

Mesangium: Matrix-increase and mesangial cell proliferation:

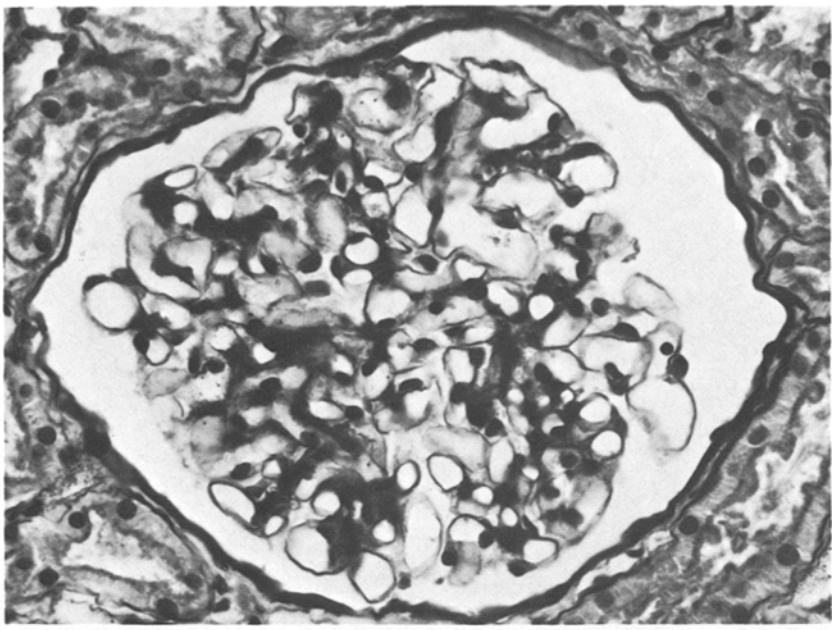
Matrix	∅	(+)	+	+	++	+	++	+++
cells	∅	(+)	(+)	+	+	++	++	++
	2%	3%	15%	40%	34%	1%	3%	2%

Extension of the glomerular lesions:

Diffuse	Diffuse with focal/segmental accentuation		Diffuse with focal/segmental or focal/global scarring
	segmental proliferation	crescents	
54%	17%	4%	25%

Interstitial lesions:

Unchanged	Focal fibrosis	Focal infiltrates	Focal tubular atrophy	Focal fibrosis and infiltrates	Focal fibrosis and tubular atrophy	Focal fibrosis and infiltrates and tubular atrophy
60%	3%	1%	7%	4%	6%	19%



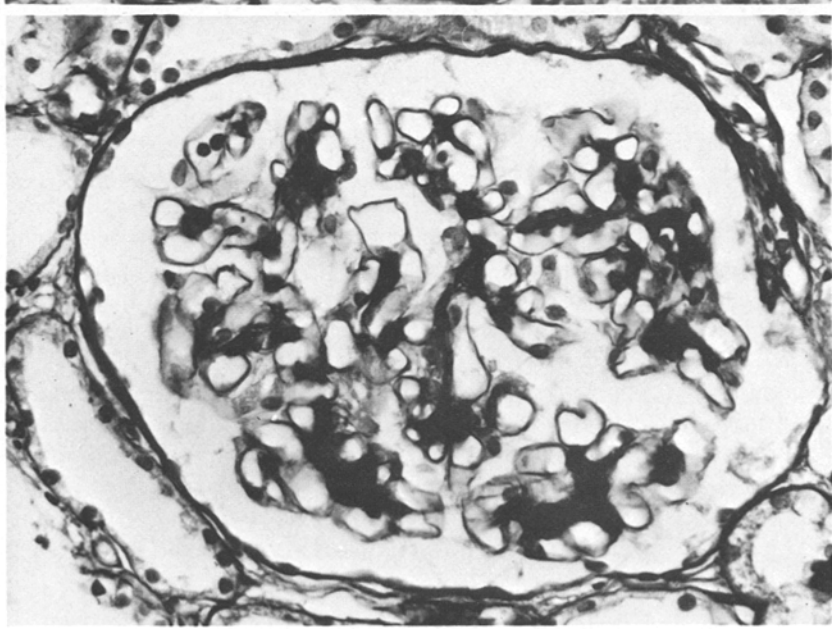


Fig. 2. "IgA-Nephropathy". Normal kidney. PAS-reaction. 460:1

Fig. 3. "IgA-Nephropathy". Minimal proliferating intercapillary glomerulonephritis. PAS-reaction. 440:1

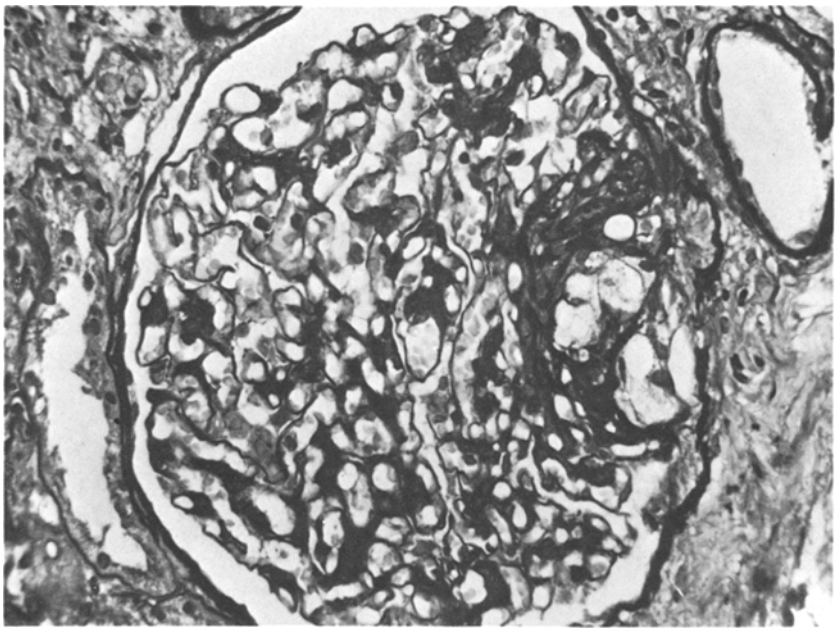


Fig. 4. "IgA-Nephropathy". Focal sclerosing glomerulonephritis. PAS-reaction, 360:1

partly homogenous (Fig. 1d), partly striped, doubly contoured (Fig. 1e), partly coarsely granular (Fig. 1f) and lumpy (Fig. 1g). In 24.2% of the cases an additional fluorescence extending into the adjacent-glomerular loops is observed (Fig. 1h). Excluding some cases with severe glomerular scarring with a focal/global or diffuse/segmental distribution of deposits, the fluorescence pattern in all other cases is diffuse and global, i.e., involving all glomeruli and each one in its entirety. In 41% of the cases IgA+C3 deposits can be detected (Table 1), in 54% deposits of IgA together with other immunoglobulins +C3 are found. An isolated deposition of IgA and/without other immunoglobulins is remarkably seldom observed (Table 1). Among the additionally deposited immunoglobulins IgG predominates, in the majority of the cases as the combination: IgA+IgG+IgM+C3. IgM is the second most frequently deposited immunoglobulin and in certain cases IgE is also observed. C1q and C4, on the other hand, are never detected (Table 1). In comparison to IgA the fluorescence of the other immunoglobulins and C3 is less intensive.

2. Histology

2.1. Light Microscopic Examinations. As can be seen in Table 2, the morphologic changes accompanying the immunohistologic diagnosis of IgA-Nephropathy vary. In the majority of the cases a mild (40%) (Fig. 5a) or moderately severe (31%) (Fig. 5b) mesangioproliferative Gn is observed. The typical immunohisto-

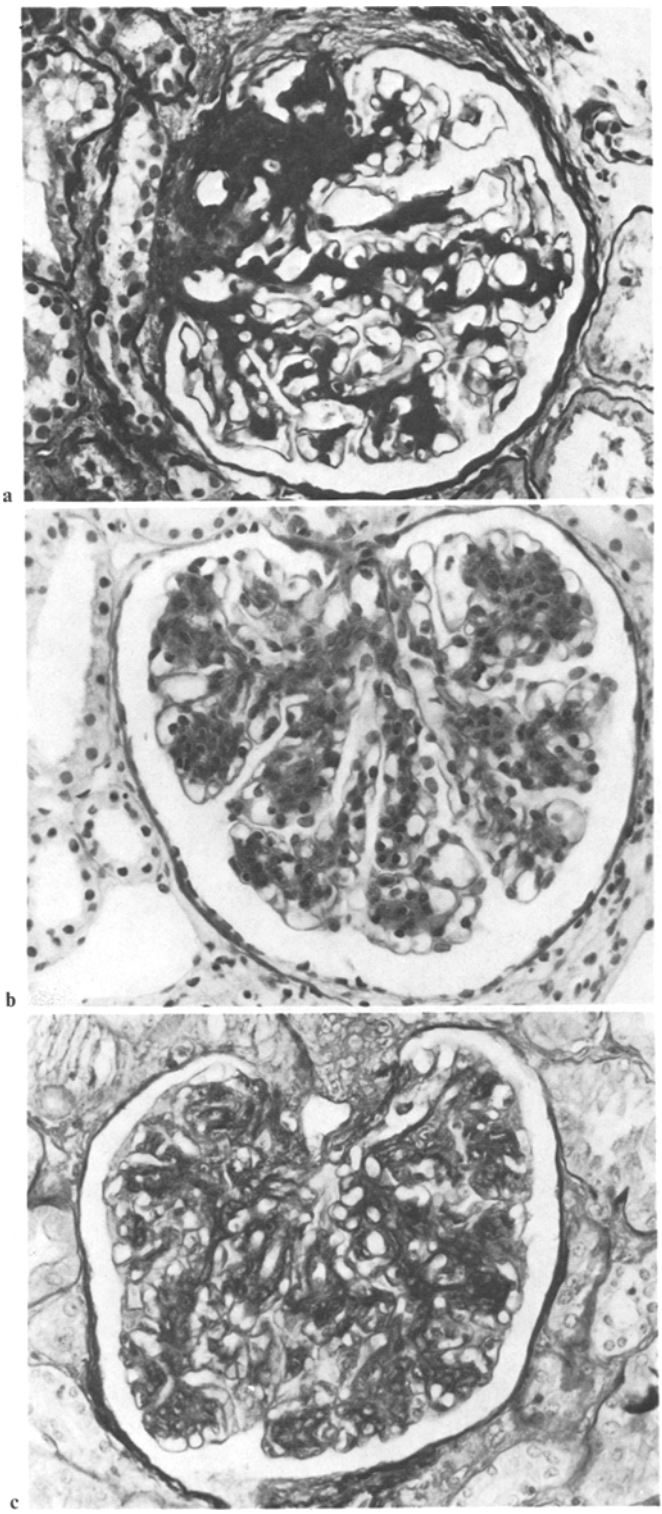


Fig. 5a–c.
"IgA-Nephropathy". Mesangioproliferative glomerulonephritis.
a Mild mesangioproliferative glomerulonephritis. PAS-reaction. 400:1
b Moderately severe mesangioproliferative glomerulonephritis. PAS-reaction. 400:1
c Severe mesangioproliferative glomerulonephritis. PAS-reaction. 360:1

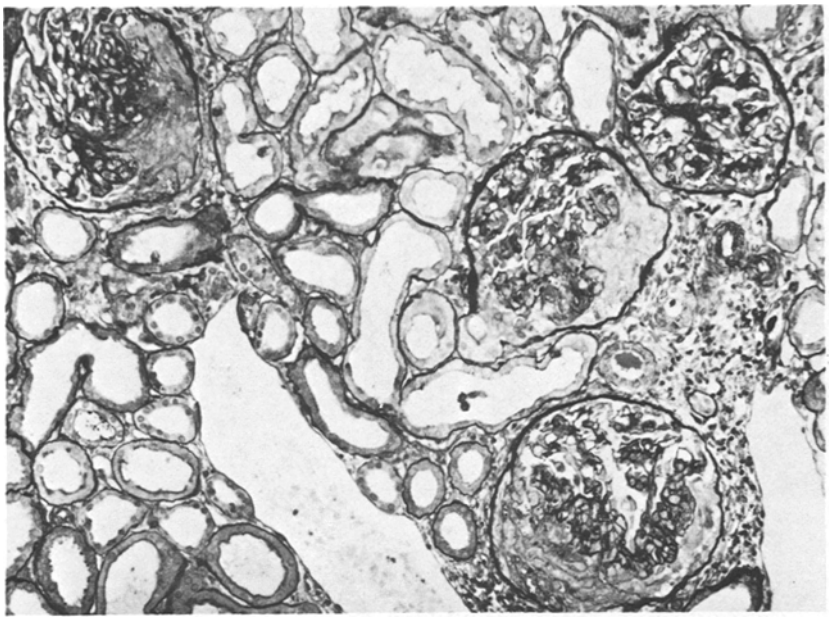


Fig. 6. "IgA-Nephropathy". Mesangioproliferative glomerulonephritis with crescents. PAS-reaction. 160:1

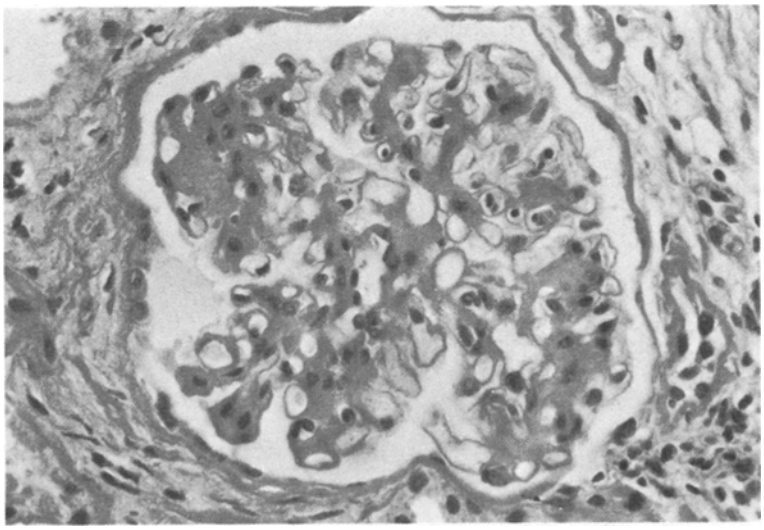


Fig. 7. "IgA-Nephropathy". Predominance of mesangial matrix compared to the mesangial cell proliferation. PAS-reaction. 460:1

logic pattern with dominating mesangial IgA deposits is also found, however, in certain cases with histologically normal findings (Fig. 2) or minimal changes (Fig. 3), in focal sclerosing glomerulonephritis (Fig. 4), in severe mesangioproliferative Gn (Fig. 5c) and in mesangioproliferative Gn with focal and diffuse crescents (Fig. 6). Although in most cases slight mesangial cell proliferation

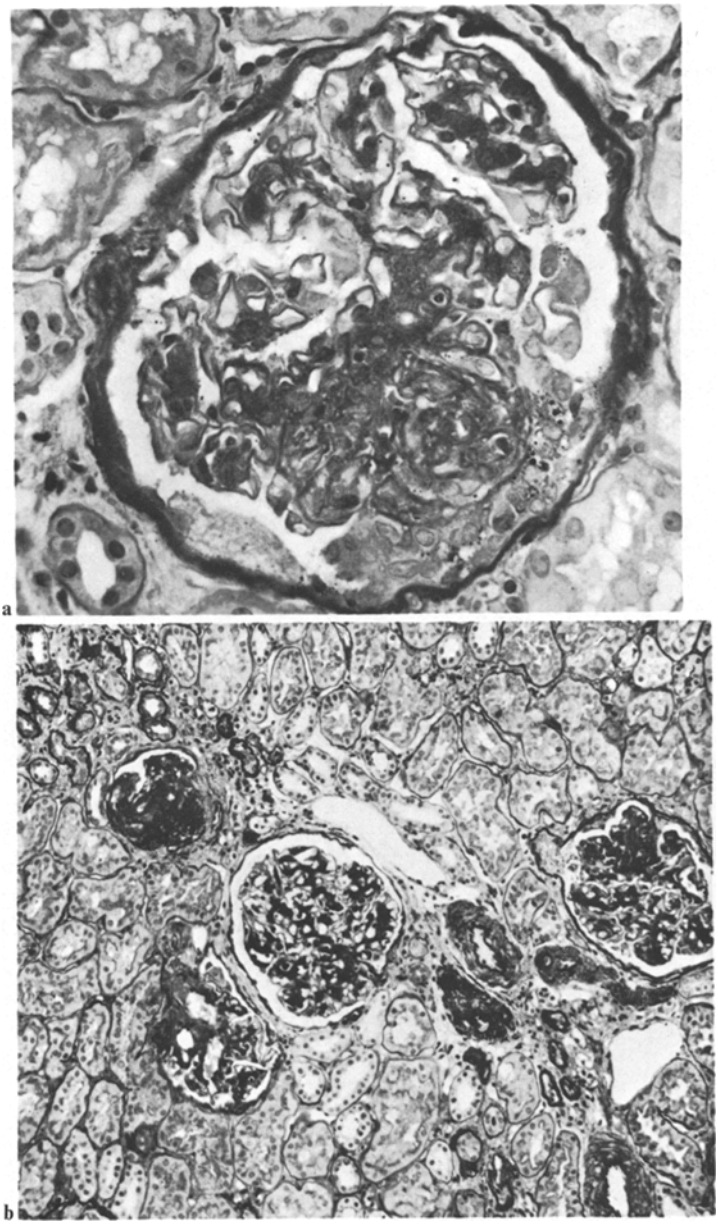


Fig. 8a and b. "IgA-Nephropathy". Mesangioproliferative glomerulonephritis with focal accentuation (segmental proliferation and crescent formation) (**a**) and with focal/segmental scarring (**b**). PAS-reaction 400:1 (**a**) 115:1 (**b**)

and increase of the matrix are both noted the latter is found to be more extensive in 51% of the cases as revealed by the PAS-reaction (Fig. 7).

The morphologic changes in the glomeruli with mesangial cell proliferation and matrix increase are diffuse, in some cases the individual glomerulus is affected to different degrees. In 21% of the cases an additional focal accentuation is noted, mostly as a focal segmental proliferation in parts of the glomerular loops (17%) (Fig. 8a), in certain cases, as small crescents and adhesions of the adjacent loops (4%). Focal-segmental or focal-global glomerular scarring is present in 25% of the cases (Fig. 8b). The interstitium is unaffected in the majority of the cases, in 32%, mainly those with moderately severe and severe mesangioproliferative Gn, a focal interstitial fibrosis of varying severity with or without tubular atrophy and cellular infiltrates is detected. Additional vascular changes in the form of a mild benign nephrosclerosis are noted in 22% of the cases.

2.2. Electron Microscopic Examinations. Corresponding to the immunohistologic findings, the electron micrographs obtained from the 23 cases investigated reveals an increase of the mesangium. Electron dense deposits are found between the mesangial cells and occasionally in a subendothelial position in the otherwise normal basement membrane. The endothelial cells are intact, whereas in some parts the foot processes of the epithelial cells are disappeared (Fig. 9a and b).

3. Comparison of Histology and Immunohistology (Table 3a and 3b)

The fluorescence pattern of IgA deposited with other immunoglobulins +C3 more often includes the adjacent loops than pure IgA or IgA +C3 deposits and is somewhat more frequently noted in cases with normal findings and minimal changes. In contrast, isolated IgA or IgA +C3 deposits are located almost entirely in the mesangium and are more often associated with a mild mesangioproliferative GN. The frequency distribution of immunoglobulins and C3 deposits is the same among the varying degrees of severity of mesangioproliferative GN; only cases with minimal changes exhibit more IgG deposits (Table 3a, 3b).

II. Clinical Findings

1. Age and Sex (Fig. 10)

The average age at the time of biopsy is 30 years (6–54 years), whereby $^2/_3$ of the patients are between 21 and 40 years old. Males clearly predominate over females by 80% to 20%.

2. Previous Diseases (see Table 4)

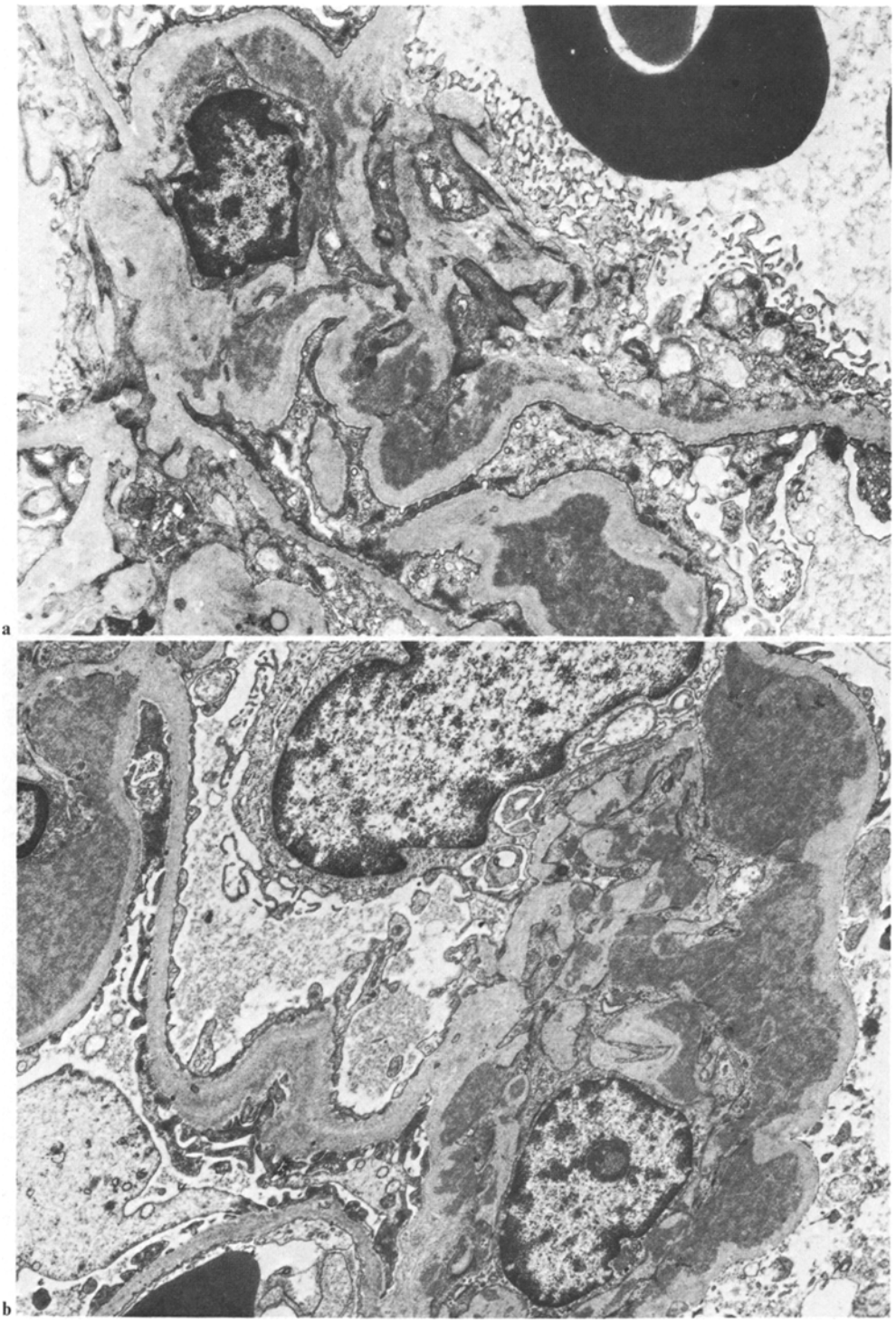


Fig. 9. a "IgA-Nephropathy". Electron micrograph with electron dense deposits in the mesangium between the mesangial cells and partly in a subendothelial position. 10,000:1. **b** "IgA-Nephropathy". Electron micrograph with electron dense deposits in the mesangium between the mesangial cells. 9,000:1

Table 3

a) Comparison of the nature and localization of the immunohistologic positive deposits with the histologic lesions in 166 renal biopsies with "IgA-Nephropathy"

	Deposits of isolated IgA or IgA and C_3 $n=75$ (45%) IgA = 8% IgA + C_3 = 92%	Combined deposits of IgA and other immunoglobulins and/without C_3 $n=91$ (55%) IgA + IgG = 1% IgA + IgM = 1% IgA + IgE + C_3 = 5% IgA + IgM + C_3 = 12% IgA + IgG + C_3 = 36% IgA + IgG + IgM + C_3 = 45%
Immunohistologic findings: Localization		
Purely mesangial	81%	72%
Mesangial, including adjacent capillary loops	19%	28%
Histologic findings:		
Normal kidney	–	4%
Minimal proliferating inter-capillary Gn	13%	21%
Mesangioproliferative Gn:		
mild	43%	35%
moderately severe	31%	33%
severe	7%	3%
Mesangioproliferative Gn with focal or diffuse crescents	6%	4%

b) Nature and frequency of the immunoglobulin- and C_3-deposits in relation to the degree of severity of the histologic lesions in minimal proliferating intercapillary glomerulonephritis, mild, moderately severe and severe mesangioproliferative glomerulonephritis ($n=147$)

	IgA	IgG	IgM	IgE	C_3
Minimal proliferating intercapillary Gn	27 (100%)	17 (69%)	9 (33%)	–	25 (96%)
Mesangioproliferative Gn mild	63 (100%)	26 (41%)	19 (30%)	2 (3%)	57 (90%)
Moderately severe and severe	57 (100%)	23 (40%)	18 (32%)	–	53 (93%)

3. First Disease Symptoms (Table 4)

As can be seen in Table 4, the initial clinical symptoms of IgA-Nephropathy differ. Macrohematuria, sometimes accompanied by proteinuria, and microhematuria usually along with proteinuria, are most often observed.

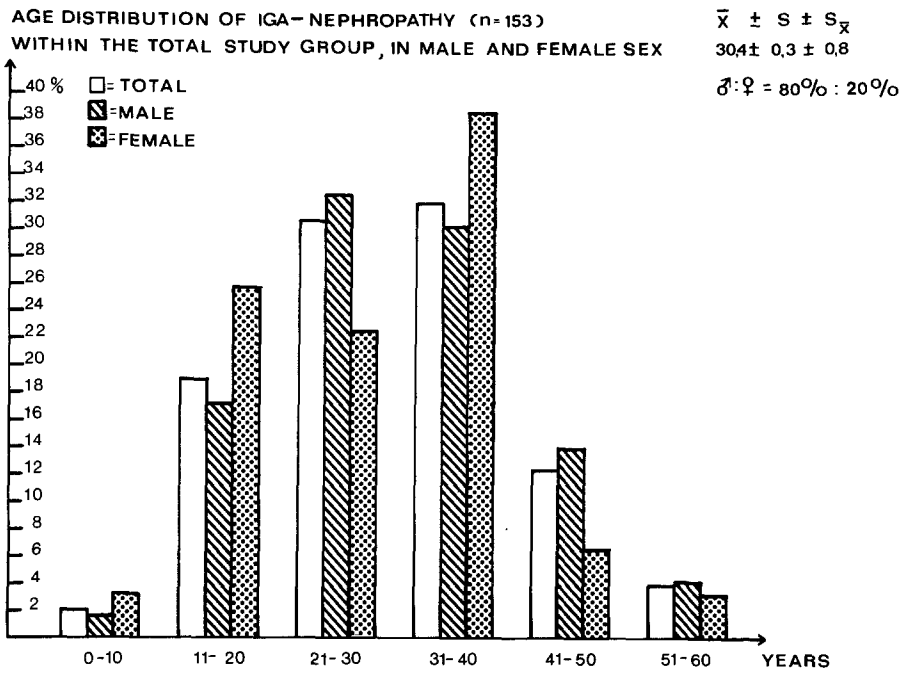


Fig. 10. "IgA-Nephropathy". Age distribution in the total study group and in relation to the sex

4. Duration of the Disease (Period Between the First Renal Symptom and the Renal Biopsy)

The first renal biopsy after appearance of the disease symptoms was performed in 28% of the cases within the first 6 months, in 47% of the cases within the first year, and in 62% of the cases within the first 2 years (average interval = 37 months). The duration of the disease in 7% of the cases ranges between 10.5 and 16 years.

5. Clinical Findings at Time of Biopsy (Table 4)

As can be seen in Table 4, a moderately severe to severe hematuria is evident in most patients along with a mild proteinuria and serum creatinine and blood pressure values in the normal or upper normal range. The AST is elevated in 21% of the cases. Serum immunoglobulin-levels are normal in 7 out of the 18 cases (39%) examined. 4 cases show an elevation of IgA and 2 cases an increase in IgG along with IgA. IgG is elevated in one case, in 2 cases IgM is decreased. The serum complement values determined in 45 cases are reduced in 13 cases (29%). Excluding a few cases which were treated with antibiotics, antiphlogistics and diuretics, most patients received no therapy prior to biopsy.

Table 4. Clinical findings in 153 patients (166 renal biopsies) with "IgA-Nephropathy"

I. Previous diseases	
1. None	25%
2. Respiratory tract infections up to 8 weeks before onset of the disease	32%
3. Respiratory tract infections without respect to time	21%
4. Renal diseases (no Gn)	7%
5. Others	15%
II. First symptoms of the disease	
1. Proteinuria	15%
2. Macrohematuria	28%
3. Macrohematuria and proteinuria	8%
4. Microhematuria	12%
5. Microhematuria and proteinuria	22%
6. Uncharacteristic symptoms	12%
7. Hypertension	3%
III. Duration of the disease (1. renal symptom – biopsy)	
$\bar{x} \pm s \pm s_{\bar{x}}$: $37 \pm 45 \pm 4$ (months)	
IV. Clinical picture at the time of biopsy	
1. Blood pressure (mm Hg): $\bar{x} \pm s \pm s_{\bar{x}}$	
RR systolic: $143 \pm 21 \pm 2$ (>160 mm Hg: 12%)	
RR diastolic: $94 \pm 12 \pm 1$ (> 95 mm Hg: 30%)	
2. Proteinuria (g/die): $\bar{x} \pm s \pm s_{\bar{x}}$	
$1.3 \pm 1.5 \pm 0.1$ (18 cases without proteinuria)	
0–1 g/die: 62%	
1–3 g/die: 30%	
> 3 g/die: 8%	
3. Hematuria:	
none: 6%	
mild (+): 28%	
moderately severe (++): 30%	
severe and macrohematuria (+++): 36%	
4. Nephrotic syndrome: 12%	
5. Serum creatinine (mg%): $\bar{x} \pm s \pm s_{\bar{x}}$	
$1.3 \pm 1.1 \pm 0.1$	
0–1 mg% = 41%	
1.1–1.4 mg% = 40%	
1.5–3.0 mg% = 17%	
3.0–9.4 mg% = 2%	
6. Creatinine-clearance (ml/min/1,73 m^2)	
80–100, >100: 71%	
60– 79: 19%	
40– 59: 4%	
< 40: 6%	

$\bar{x}$ = means, s = SD (standard deviation), $s_{\bar{x}}$ = SEM (standard error of the mean)

Table 5. Histologic, immunohistologic and clinical findings in relation to the sex (♂:♀=80%:20%) in 153 patients with "IgA-Nephropathy"

	♂ $n=122$	♀ $n=31$
I. Histology		
Normal kidney	2%	3%
Minimal proliferating intercapillary Gn	14%	31%
Mesangioproliferative Gn		
mild	41%	33%
moderately severe	33%	23%
severe	5%	3%
Mesangioproliferative Gn with focal and diffuse crescents	4%	7%
Focal sclerosing Gn	1%	–
II. Immunohistology		
1. Localization:		
purely mesangial	80%	58%
mesangial including adjacent capillary loops	20%	42%
2. Nature of deposits:		
IgA and other immunoglobulins	4%	10%
IgA and C_3	44%	29%
IgA and other immunoglobulins and C_3	52%	61%
III. Clinical manifestations		
1. Previous diseases:		
respiratory tract infections	37%	23%
2. First symptoms of the disease:		
Proteinuria	12%	19%
Macrohematuria	32%	12%
Microhematuria	11%	19%
Macrohematuria and Proteinuria	4%	19%
Microhematuria and Proteinuria	24%	27%
Uncharacteristic symptoms	14%	4%
Hypertension	3%	–
3. Clinical picture at the time of biopsy		
AST 200 IE	25%	4%
Blood pressure (mm Hg): $x \pm s \pm s_{\bar{x}}$		
RR systolic	$141 \pm 21 \pm 2$	$139 \pm 23 \pm 4$
RR diastolic	$95 \pm 12 \pm 1$	$90 \pm 13 \pm 2$
Proteinuria (g/die): $\bar{x} \pm s \pm s_{\bar{x}}$	$1.3 \pm 1.4 \pm 0.1$	$1.6 \pm 1.8 \pm 0.4$
Nephrotic syndrome	11%	17%
Serum-creatinine (mg%): $\bar{x} \pm s \pm s_{\bar{x}}$	$1.36 \pm 1.2 \pm 0.1$	$1.14 \pm 0.5 \pm 0.1$
Hematuria		
none	6%	3%
mild (+)	28%	30%
moderately severe (++)	31%	27%
severe and macrohematuria (+++)	35%	40%

x=means, s=SD (standard deviation), $s_{\bar{x}}$=SEM (standard error of the mean)

6. Morphologic and Clinical Findings in IgA-Nephropathy in Relation to Sex

6.1. Age (Fig. 10). With the same average age, females are percentually more predominant than males in the 11–20 and 31–40 age groups, whereas the frequency peak of males occurs between 21–30 years of age.

6.2. Histology and Immunohistology (Table 5). As Table 5 shows, the histologic changes in males are more severe than in females; immunohistologically, more IgA+C3 deposits, mainly of a mesangial type are found in males, whereas in females combined deposits of IgA, other immunoglobulins and C3 dominate and the fluorescence pattern more often includes adjacent capillary loops.

6.3. Clinical Manifestations (Table 5). As can be seen in Table 5, the disease in males begins in most cases with macrohematuria, whereas in females proteinuria, microhematuria or macrohematuria plus proteinuria are more often observed as the initial symptoms. With a similar average duration of the disease the clinical picture at the time of biopsy does not differ significantly between sexes.

7. Histologic and Clinical Picture of the Disease at the Time of Biopsy in Relation to the First Symptoms

As can be observed in Table 6 the disease manifests itself differently. Although the duration of the disease is on the average the same in all symptom groups, cases in which a proteinuria is found at onset of the disease show the most severe histologic as well as clinical picture at the time of biopsy. If a macrohematuria is the first symptom, the glomerular changes are milder and with the exception of the severe hematuria characterizing the majority of cases the clinical parameters at the time of the biopsy are normal. The mildest histologic as well as clinical expression of the disease occurs when a microhematuria is the first symptom. When microhematuria and proteinuria are the first symptoms the histologic picture shows more severe histologic changes than compared to the symptom group "macrohematuria+proteinuria". The clinical picture is marked by elevated blood pressure, microhematuria and mild proteinuria.

8. Comparison of the Histologic Degree of Severity with the Immunohistologic and Clinical Picture (Table 7)

8.1. Immunohistology. Whereas the type of deposits is independent of the histologic degree of severity a purely mesangial location of immunodeposits is more often found with more severe glomerular changes.

8.2. Histology. Focal accentuations as well as glomerular scarring and interstitial fibrosis occur more frequently in the moderately severe and severe mesangioproliferative GN.

Table 6. Histologic and clinical picture of the disease at the time of biopsy in relation to the first symptom of the disease in 153 patients (166 renal biopsies) with "IgA-Nephropathy"

First symptom	Proteinuria $n=20$	Macrohematuria $n=37$	Microhematuria $n=16$	Macrohematuria and proteinuria $n=11$	Microhematuria and proteinuria $n=32$	Uncharacteristic symptoms $n=16$
Sex: ♂:♀	75%:25%	89%:11%	69%:31%	55%:45%	81%:19%	94%:6%
1. Histology						
Normal kidney	–	–	–	–	4%	6%
Minimal proliferating intercapillary Gn and mild mesangioproliferative Gn	40%	57%	88%	73%	54%	50%
Moderately severe and severe mesangioproliferative Gn	50%	34%	12%	18%	39%	38%
Mesangioproliferative Gn with crescents	10%	6%	–	9%	3%	6%
Focal sclerosing Gn	–	3%	–	–	–	–
2. Clinical manifestations						
Hematuria						
none	15%	–	–	9%	6%	7%
mild (+)	40%	13%	19%	18%	29%	33%
moderately severe (++)	40%	30%	37%	27%	39%	27%
severe and macrohematuria (+++)	5%	57%	44%	46%	26%	33%
Blood pressure (RR) (mm Hg): $\bar{x}\pm s\pm s_{\bar{x}}$						
RR systolic	150 ±22 ±5	136 ±15 ±3	136 ±16 ±4	130 ±13 ±4	150 ±23 ±4	139 ±24 ±6
RR diastolic	95 ±11 ±3	89 ±11 ±2	90 ± 8 ±2	85 ± 4 ±1	97 ±13 ±2	90 ±12 ±3
Proteinuria (g/die): $\bar{x}\pm s\pm s_{\bar{x}}$	2.3± 2.1±0.5	0.9±0.9 ±0.2	0.7± 0.6±0.2	2.1± 2.3±0.8	1.1± 0.9±0.2	1.8± 2.2±0.6
Nephrotic syndrome	40%	3%	–	27%	9%	18%
Serum-creatinine (mg%): $\bar{x}\pm s\pm s_{\bar{x}}$	2.4± 2.7±0.6	1.1±0.3 ±0.04	1.0± 0.4±0.1	1.3± 0.5±0.2	1.1± 0.4±0.1	1.3±0.9±0.2

$\bar{x}$=means, s=SD (standard deviation), $s_{\bar{x}}$=SEM (standard error of the mean)

Table 7. Immunohistological and clinical picture of "IgA-Nephropathy" in relation to different degrees of severity of glomerular lesions ($n=147$)

	Minimal proliferating intercapillary Gn and mild mesangio-proliferative Gn ($n=90$)	Moderately severe and severe mesangio-proliferative Gn ($n=57$)
Sex ♂:♀	79%:21%	88%:12%
I. Immunohistology		
Localization:		
purely mesangial	80%	95%
mesangial including adjacent capillary loops	20%	5%
Nature of deposits		
IgA and other immunoglobulins	5%	5%
IgA and C_3	41%	43%
IgA and other immunoglobulins and C_3	54%	52%
II. Histology		
Extension of glomerular lesions		
diffuse	61%	21%
diffuse with focal/segmental accentuation	4%	30%
scarring (foc./segm. and foc./glob.)	35%	49%
Interstitial lesions		
fibrosis	20%	49%
III. Clinical manifestations		
Duration of the disease (months): $\bar{x}\pm s\pm s_{\bar{x}}$	$33\pm41\pm5$	$53\pm54\pm8$
Blood pressure (RR) (mm Hg): $\bar{x}\pm s\pm s_{\bar{x}}$		
RR systolic	$138\pm19\pm2$	$151\pm23\pm3$
RR diastolic	$90\pm11\pm1$	$98\pm13\pm2$
Hematuria:		
none	6%	6%
mild (+)	29%	31%
moderately severe (++)	30%	25%
severe and macrohematuria (+++)	35%	38%
Proteinuria (g/die): $\bar{x}\pm s\pm s_{\bar{x}}$	$0.9\pm0.8\pm0.1$	$1.5\pm1.5\pm0.2$
Nephrotic syndrome	2%	20%
Serum-creatinine (mg%): $\bar{x}\pm s\pm s_{\bar{x}}$	$1.1\pm0.3\pm0.03$	$1.5\pm1\pm0.1$

$\bar{x}$=means, s=SD (standard deviation), $s_{\bar{x}}$=SEM (Standard error of the mean)

8.3. Clinical Manifestations. Along with a significantly longer duration of the disease the clinical manifestations with regard to RR, proteinuria, NS and serum creatinine are more severe in moderately severe and severe mesangioproliferative GN, whereas the degree and frequency of hematuria at the time of biopsy show no relationship to the severity of glomerular changes.

9. Comparison of the Type of Immunohistologic Deposits with the Clinical Picture

Whereas the histologic findings vary slightly with the type and extent in relation to the immunohistologic pattern, the clinical manifestations at the time of the biopsy do not vary.

10. Observations on the Course of the Disease (Serial Renal Biopsies)

After an average of one year rebiopsies carried out on 14 patients show in 5 cases findings comparable to those at the first biopsy (1 case with MPI, 2 cases with mild mesangioproliferative GN, 2 cases with moderately severe mesangioproliferative Gn), in 5 cases an improvement (1 case from moderately severe mesangioproliferative Gn to normal renal findings, 2 cases from mild mesangioproliferative GN to MPI, 2 cases from moderately severe to mild mesangioproliferative Gn), and in 4 other cases a deterioration of the histologic findings (4 cases from mild to moderately severe). The clinical course of the disease corresponds largely with the histologic course. Of the 4 cases with histologic deterioration 2 developed hypertension; in the 2 other cases the clinical findings remained unchanged. The immunohistologic findings showed no change during the course of the disease.

Discussion

In accordance with the reports of other authors (Morel-Maroger et al., 1972; Lowance et al., 1973; De Werra et al., 1973; McCoy et al., 1974) the immunohistologic findings of the present study justify defining the IgA-IgG-Nephropathy, reported for the first time by Berger (1968, 1969), as a special immunohistologic form characterized by a dominating mesangial deposition of IgA. With the exception of individual cases with glomerular scarring, a diffuse and global mesangial fluorescence pattern of varying intensity is found involving all glomeruli and extending out into the entire glomerulus. Depending on the quantity of deposits the fluorescence pattern can be described, in agreement with Thoenes (1976), as either arborescent or spotted, whereby the deposits have a partly granular, partly striped, doubly contoured or homogenous character. In some cases an extension of the mesangial deposit pattern into adjacent capillary loops is observed by us, as well as by Levy et al. (1973), Lowance et al. (1973), De Werra et al. (1973), McCoy et al. (1974), Clarkson et al. (1977) and Shirai et al. (1978). The characteristic immunohistologic pattern can be confirmed by the electron microscopic findings in accordance with Druet et al. (1970), Davies et al. (1973), Levy et al. (1973), McCoy et al. (1974) and Churg and Grishman (1976).

Whereas an isolated deposition of IgA is rarely detected, confirming the findings of Berger (1969), De Werra et al. (1973) and Shirai et al. (1978), IgA

is deposited in most cases together with other immunoglobulins and/or C3, in $^1/_4$ of the cases or more often in the form of combined deposits of IgA + IgG + IgM + C3, as also shown by Lowance et al. (1973), McCoy et al. (1974), Zimmerman and Burkholder (1975), Shirai et al. (1978) and in some cases also in the form of IgA + IgM + C3, in agreement with Druet et al. (1970), Lowance et al. (1973) and Shirai et al. (1978), or as IgA + IgE + C3. The combined deposition of IgA + IgG + C3 observed in the majority of their cases by Berger (1969), McEnery et al. (1973) and Sissons et al. (1975), could neither be confirmed by us, nor by Clarkson et al. (1977) and Shirai et al. (1978). On the contrary we observe a deposition of IgA as a single immunoglobulin together with C3 in most of the cases in agreement with both Clarkson et al. (1977) and Shirai et al. (1978). Similar to the findings of McCoy et al. (1974) and Sissons et al. (1975) the complement components C1q and C4 were never detected whereas Clarkson et al. (1977) as well as Shirai et al. (1978) demonstrated C1q and C4 in some cases. As also demonstrated by De Werra et al. (1973), McCoy et al. (1974) and Shirai et al. (1978), the fluorescence of IgA is the most intensive, whereby the fluorescence pattern more often includes adjacent loops when additional immunoglobulins are deposited, in agreement with De Werra et al. (1973). Since in the so-called IgA-IgG Nephropathy, IgA is both the dominant and only consistently demonstrable immunoglobulin and further because evidence for on inflammatory glomerular reaction upon the mesangial IgA-deposits is not obligatory, we prefer the designation of IgA-Nephropathy to describe this disease entity, as well as McCoy et al. (1974), Clarkson et al. (1977) and Shirai et al. (1978).

The immunohistologic findings suggest an uniform morphologic-clinical picture of the disease. However, this homogenous immunohistologic picture of IgA-Nephropathy contrasts with a broad histologic spectrum observed microscopically, in accordance with Davies et al. (1973), Lowance et al. (1973), McCoy et al. (1974), Clarkson et al. (1977), Shirai et al. (1978) and Yokoska et al. (1978), including normal findings (Berger, 1969, McCoy et al., 1974) and minimal changes (Levy et al., 1973), mesangioproliferative Gn with focal (Levy et al., 1973), as well as with diffuse crescents and one case with focal sclerosing Gn.

The present study confirms our previous findings (Gärtner et al., in press) that most of the cases belong to the group of mild and moderately severe mesangioproliferative Gn and comprise collectively 31% of the mesangioproliferative Gn cases in our study group. When one examines the distribution of IgA-Nephropathy amongst the various groups of mesangioproliferative Gn, as defined by their severity, one observes a quite equal incidence of IgA-Nephropathy in the different degrees of severity. These results indicate that the typical immunohistologic picture of the mesangial IgA-deposits do not correlate with an uniform morphologic picture. Although many authors associate the morphologic changes in IgA-Nephropathy with a focal proliferative Gn (Berger and Hinglais, 1968; Berger, 1969; Morel-Maroger et al., 1972; De Werra et al., 1973; Levy et al., 1973; McCoy et al., 1974) we believe, that the glomerular changes involve diffuse morphologic processes with a predominantly mild to moderately severe mesangial cell proliferation and matrix increase (Druet et al.,

1970; Maintz et al., 1972; Sissons et al., 1975; Clarkson et al., 1977; Shirai et al., 1978; Yokoska et al., 1978). Confirming the results of Maintz et al. (1972), De Werra et al. (1973), Zimmerman and Burkholder (1975) and Shirai et al. (1978) the more extensive accentuation of the mesangial matrix in comparison to mesangial cell proliferation, observed in several cases, already suggests the diagnosis of IgA-Nephropathy. Along with this diffuse morphologic process a focal accentuation is found in 20% of the cases. This and the varying degrees of diffuse morphologic changes occasionally found in various glomeruli, establish the impression of a focal proliferative Gn. Because the frequency of the lesions with focal accentuation increases with increasing severity of the diffuse glomerular changes, and because in cases with minimal glomerular changes focal changes are not observed, the latter can not be considered as the most minor histologic lesion, in agreement with McEnery et al. (1973). In accordance with Berger et al. (1975) no relationship exists between the quantity of mesangial deposits and the severity of the glomerular histologic findings. The immunohistologic picture also shows no differences with regard to the extension and nature of the deposits or frequency of the deposited immunoglobulins among the various degrees of severity of mesangioproliferative Gn. Only in minimal changes one can observe more cases with a fluorescence pattern extending into the adjacent capillary loops and with more frequent deposits of IgA together with other immunoglobulins and C3.

In accordance with the findings of Druet et al. (1970), Maintz et al. (1972), Davies et al. (1973), Levy et al. (1973), Lowance et al. (1973), McEnery et al. (1973), Sissons et al. (1975), Clarkson et al. (1977) and Shirai et al. (1978), the immunohistologic picture of IgA-Nephropathy is found predominantly in males. This distinct dominance however does not seem to be due to the subjects selected for our study (army), because the male sex predominates also in childhood (Levy et al., 1973, McEnery et al., 1973). The average age of patients with IgA-Nephropathy (31 years) in our study corresponds to that reported by Berger (1969), Druet et al. (1970), Lowance et al. (1973), McCoy et al. (1974), Clarkson et al. (1977) and Shirai et al. (1978), and is the same in males as in females. Females are somewhat more frequently represented in the younger age groups. Whereas the disease begins primarily with a recurring macrohematuria (Levy et al. 1973) in children, it manifests itself differently in adults without specific features, in agreement with De Werra et al. (1973), Lowance et al. (1973), Sissons et al. (1975) and Clarkson et al. (1977). However, hematuria predominates as a first symptom, expressed either as macrohematuria accompanied by a proteinuria, as observed especially in females, or as microhematuria, in most cases together with a proteinuria, also found by De Werra et al. (1973), Lowance et al. (1973), Sissons et al. (1975), Clarkson et al. (1977). Nevertheless, in agreement with De Werra et al. (1973), the disease begins in some cases with an isolated chance proteinuria, with uncharacteristic symptoms (fatigue, headache) or occasionally with hypertension (McCoy et al., 1974). As also reported by other authors (Levy et al., 1973; De Werra et al., 1973; McCoy et al., 1974; Sissons et al., 1975; Clarkson et al., 1977) respiratory tract infections were observed in some cases directly before the beginning of the disease, primarily in those who later developed a proteinuria or a macrohematuria and proteinuria.

At the time of biopsy (on average 3 years after the 1st symptom) the disease is characterized in most cases by hematuria of varying severity, by a mild proteinuria, but seldom by a nephrotic syndrome and by average blood pressure and creatinine values approaching the upper normal range, in accordance with Berger and Hinglais (1968), Maintz et al. (1972), De Werra et al. (1973), McCoy et al. (1974) aand Clarkson et al. (1977). No significant differences exist between males and females although the first symptoms vary, the immunohistologic picture shows slight distinctions and the morphologic changes in the female are less severe.

Comparing the first symptoms with the clinical picture at the time of biopsy shows that the first symptoms permit a statement as to the severity of the disease. The mildest course would therefore be expected with asymptomatic microhematuria at the onset of the disease, whereas proteinuria as first symptom would indicate the most severe histologic and clinical picture. The nature and localization of the immunoglobulin- and complement deposits allow no conclusions to be made as to the severity of the disease, confirming the findings of Bürkle et al. (1976) and Clarkson et al. (1977). A positive relationship exists however between histologic severity and clinical manifestations, in accordance with Shirai et al. (1978).

Whereas minimal changes and mild mesangioproliferative Gn do not differ, the 2 forms together can be differentiated from the group of moderately severe and severe mesangioproliferative Gn with regard to blood pressure, serum-creatinine, proteinuria and nephrotic syndrome. Only the severity of hematuria at the time of biopsy seems to be independent of the degree of histologic changes in contrast to Shirai et al. (1978), who observed a macrohematuria more often in connection with mild morphologic lesions.

With the exception of some cases (Berger, 1969; Druet et al., 1970; Lowance et al., 1973; Sissons et al., 1975), it was the notion until recently that patients suffering from an IgA-Nephropathy with mesangial IgA deposition exhibited a particularly favorable prognosis (Maintz et al., 1972; Morel-Maroger et al., 1972; Davies et al., 1973; De Werra et al., 1973; McCoy et al., 1974; Berger et al., 1975; Bürkle et al., 1976); indeed this study also being suggestive of a positive course for the discase. However, this opinion of a prognostically favorable course seems to be doubtful and to be attributable to the short observation periods in these studies since the more recent results of Van der Peet et al. (1977) have demonstrated that over a longer observation period (4 years) the majority of cases, and most particularly elderly patients, exhibited a progressive renal insufficiency.

To consolidate a diagnosis of an IgA-Nephropathy only on the basis of clinical manifestations is not possible, since the disease exhibits a wide spectrum of unspecific, heterologous clinical symptoms either at the onset of the disease and at the time of biopsy.

Just how unspecific the clinical picture of this disease is has also been outlined by the work of Yokoska et al. (1978), wherein no clear differences could be identified between cases of IgA-Nephropathy and a control group of patients exhibiting a mild mesangioproliferative Gn without IgA deposition.

The lack of correlation between the clinical manifestations of the disease and

mesangial IgA deposition is also demonstrated by our findings. Thus our group of patients suffering from IgA-Nephropathy also showed on average no clear clinical differences when compared with groups of patients showing either a mild mesangioproliferative Gn with different immunofluorescence patterns or immunohistologically negative cases with various morphologic degrees of severity from our total sample of mesangioproliferative Gn (Gärtner et al., in press). Furthermore, the results of Van de Putte et al. (1974) as well as those of Nomoto et al. (1974) emphasize how a recurrent hematuria is not specific for IgA-Nephropathy and do not justify the diagnosis of IgA-Nephropathy although it seems to be in general a characteristic symptom of this condition. Thus these authors reported that immunohistologic examination of patients with recurrent hematuria revealed no cases exhibiting a simultaneous IgA deposition. Considering their results, in addition to those of Kupor et al. (1975) who showed in a similar study only a few patients with intramesangial IgA deposits, we are lead to the conclusion that a recurrent hematuria (macrohematuria) is not definitively diagnostic of an IgA-Nephropathy, in agreement with Clarkson et al. (1977).

Although the pathogenesis of IgA-Nephropathy is still unknown, a number of features would support the notion of an immune-complex pathomechanism for the disease. Thus supportive evidence includes the observation of granular mesangial fluorescence patterns which correspond to electron-dense deposits in the mesangium and the detection of IgA deposits in kidney transplants (Berger et al., 1975). With regards to the actual pathomechanism responsible for the intramesangial IgA-deposits the following possibilities may be discussed:

1. Deposition of circulating antigen-IgA-antibody complexes in the mesangium.
2. Binding of IgA-antibodies to either exogenous or endogenous antigens located in the mesangium or with antigenic mesangial structures as antigens.
3. IgA may act as an antigen.

The latter possibility seems unlikely since anti-IgA antibodies have not been detected (Lowance et al., 1973), and in our study only IgA and C_3 were deposited in numerous cases. It is known that aggregated IgA immunoglobulin may activate C_3 by way of the alternate pathway (Götze and Müller-Eberhard, 1971). Moreover, since neither C1q nor C4 were detected in our, or other studies (Davies et al., 1973; Evans et al., 1973; Sissons et al., 1975) but rather factor B and properdine (Evans et al., 1973; McCoy et al., 1974) and we often find IgA+C3 deposits, the possibility exists in this situation that complexed IgA deposits in the mesangium activate C3 by the alternate pathway. The IgA-antibodies may have been directed against mesangium-localized antigen or mesangial antigenic structures as postulated above. Certainly our observations of rare, isolated IgA-deposits would support the foregoing contentions.

However, in more recent studies it has been shown that the Fc-fragments of monomeric IgA immunoglobulin may activate C_3 via the classical pathway (Buritt et al., 1977), an observation which may correspond to the occasional detection of both C1q and C4 in patients with IgA-Nephropathy (Clarkson et al., 1977; Shirai et al., 1978; Yokoska et al., 1978). These findings and the additional observation of the frequent deposition of IgA with other immunoglob-

ulin species would suggest that the characteristic picture of an IgA-Nephropathy exhibited immunohistologically is the result not of one, but perhaps several immunologic pathomechanisms.

Whether raised serum IgA levels have any significance in the pathogenesis of an IgA-Nephropathy must still remain an open question, since whilst some studies do demonstrate an elevation of serum IgA (Berger and Hinglais, 1968; Berger et al., 1975; Zimmerman and Burkholder, 1975; Clarkson et al., 1977; Berthoux et al., 1978) as do 4 out of 18 of our cases, other authors find no evidence for the elevation of circulating levels of this immunoglobulin (Druet et al., 1970; Maintz et al., 1972; Davies et al., 1973; Lowance et al., 1973; Brettle et al., 1978; Yokoska et al., 1978). However, the study of Sakai and Nomoto (1978) in families with cases of IgA-Nephropathy suggests that elevated IgA-levels may arise through a reduction of IgA-specific supressor T-cell activity which occurs with a concomitant increase in the number of IgA-carrying peripheral lymphocytes. Indeed the observations of Sakai and Nomoto (1978) support the work of Berthoux et al. (1978) and Noël et al. (1978), who suggest that immunogenetic factors play a role in the induction of IgA-Nephropathy. In these latter studies a significantly increased occurrence of HLA-BW35 antigen in patients with IgA-Nephropathy was observed. In the meantime corresponding findings were reported by Sabatier et al. (1979) in two HLA-identical brothers suffering from IgA-Nephropathy, in whom the HLA-BW 35-antigen also could be detected.

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