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The Size of the Juxtaglomerular Apparatus in Glomerulonephritis with the Nephrotic Syndrome

A Morphometrical Study of Renal Biopsies *

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Summary. The juxtaglomerular apparatus was histoplanimetrically studied in renal biopsies of 65 cases of membranoproliferative glomerulonephritis and 64 cases of minimal proliferative intercapillary glomerulonephritis (MPI) ("minimal changes"). The juxtaglomerular cell complex (JGC complex) consisting of the epithelioid cells (granular cells) and the Goormaghtigh's cells (agranular or lacis cells) was significantly enlarged in the nephrotic syndrome. 10 to 14 days' duration of the nephrotic syndrome was shown to be sufficient to bring about an enlargement of the JGC complex. After a successful treatment of the nephrotic syndrome with steroids, there was no enlargement of the JGC complex. The enlarged JGC complex persisted despite steroid treatment in the steroid-resistant nephrotic syndrome, although a mild suppressive effect of steroids on the size of the JGC complex was observed.

There was no significant relationship between hypertension and the size of the JGC complex.

Creatinine retention tended to be associated with an enlargement of the JGC complex.

The macula densa was not enlarged in the nephrotic syndrome, in contrast to the enlarged JGC complex.

Key words: Juxtaglomerular Apparatus — Macula Densa — Glomerulonephritis — Nephrotic Syndrome.

Zusammenfassung. Morphometrische Untersuchungen zur Größe des juxtaglomerulären Apparates bei Glomerulonephritis wurden an Nierenbiopsien von 65 Fällen mit membranoproliferativer Glomerulonephritis und 64 Fällen mit minimal proliferierender intercapillärer Glomerulonephritis (MPI) ("minimal changes") planimetrisch durchgeführt.

Die aus den epitheloiden Zellen und Goormaghtigh-Zellen bestehenden juxtaglomerulären Zellkomplexe (JGZ-Komplexe) waren bei nephrotischem Syndrom statistisch signifikant vergrößert. Das Bestehen eines nephrotischen Syndroms über 10–14 Tage erwies sich als ausreichend, um eine Vergrößerung der JGZ-Komplexe hervorzurufen. Bei klinischer Besserung des nephrotischen Syndroms infolge einer Steroidbehandlung entsprach die Größe der JGZ-Komplexe den Kontrollen. Bei steroidresistentem nephrotischem Syndrom blieben die JGZ-Komplexe, trotz der Steroidbehandlung, vergrößert, jedoch ließ sich ein geringgradiger Hemmeffekt der Steroide auf die Größenzunahme der JGZ-Komplexe bei steroid-resistentem nephrotischem Syndrom feststellen.

Ein Hypertonus hatte keinen statistisch signifikanten Einfluß auf die Größe der JGZ-Komplexe. Bei Kreatinin-Retention ergab sich eine Tendenz zur Hypertrophie der JGZ-Komplexe. Im Gegensatz zu den JGZ-Komplexen zeigten die Maculae densae keine signifikante Vergrößerung bei nephrotischem Syndrom.

In glomerulonephritis, there are several factors which may influence the activity of the juxtaglomerular apparatus, such as the nephrotic syndrome

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(Yoshinaga *et al.*, 1963; Veyrat *et al.*, 1964; Imai and Sokabe, 1968; Medina *et al.*, 1974), steroid therapy (Hartroft and Hartroft, 1953), hypertension (Tobian *et al.*, 1958; Brown *et al.*, 1964; Helmer, 1964), treatment with diuretics (Vander, 1967), abnormal electrolyte levels in the serum (Pitcock and Hartroft, 1958; Aida *et al.*, 1964; de Champlain *et al.*, 1966), and impaired renal function. The present study was undertaken to investigate morphologically the interrelationship of these factors which may act positively or negatively on the activity of the juxtaglomerular apparatus, and to determine which factors are important in glomerulonephritis. Membranoproliferative glomerulonephritis and minimal proliferative intercapillary glomerulonephritis (Bohle *et al.*, 1972) ("minimal changes" according to Habib *et al.*, 1961) were chosen for the present study, because the former often presents a steroid-resistant nephrotic syndrome with various combinations of hypertension, impaired renal function and haematuria, whilst the latter shows a steroid-responsive nephrotic syndrome, usually without either hypertension or chronic renal insufficiency (Cameron *et al.*, 1970; Churg *et al.*, 1970; White *et al.*, 1970; Habib *et al.*, 1973; West, 1973; Bohle *et al.*, 1974).

The degree of hypertrophy and hyperplasia of the juxtaglomerular cells, as well as their degree of granulation, parallels the activity of the juxtaglomerular apparatus (Goormaghtigh, 1940; Bohle *et al.*, 1953; Hartroft and Hartroft, 1953; Tobian *et al.*, 1958; Meyer, 1972). In the present study, the size of the juxtaglomerular cell complex consisting of the epithelioid cells (granular cells) and the Goormaghtigh's cells (agranular or lacis cells), and that of the macula densa were histoplanimetrically measured in order to evaluate the activity of the juxtaglomerular apparatus (Meyer, 1972). As the number of the juxtaglomerular apparatuses available in a biopsy is small, the planimetry was made on collected biopsy material in every study group. This method has been proved to be correct in a preliminary study by comparing with volumetric measurements of the juxtaglomerular cell complex on serial sections of the normal kidneys (Meyer *et al.*, to be published).

Materials and Methods

As study groups, *65 renal biopsy* cases of *membranoproliferative glomerulonephritis* and *64 of minimal proliferative intercapillary glomerulonephritis (MPI)* ("minimal changes") were selected from the biopsy files of the Institute of Pathology of the University of Tübingen. The criteria for selection were that two or more juxtaglomerular apparatuses could be observed on a biopsy section, and that precise clinical data were available. Cases showing abnormal levels of serum sodium or potassium were rare in the selection and were excluded in the present study (only 5 cases showed low levels of serum sodium in a preliminary study of 180 cases). The control group consists of 126 biopsy cases of adults ranging in age from 12 to 58 years and 23 cases of children under 12 years of age. These controls were selected from the cases diagnosed as unremarkable at the Institute of Pathology of the University of Tübingen. The criteria for selection were those described above and that blood pressure was neither over 150 mmHg systolic nor over 90 mmHg diastolic.

Wedge or needle biopsies fixed in 5% formalin, were embedded in paraffin, cut at 4 to 5 μ, and then stained with periodic-acid-Schiff stain (PAS).

Morphometry of the juxtaglomerular cell complex (JGC complex) and the macula densa (MD): Measurements of the cut-surface size of the JGC complex consisting of the epithelioid cells and Goormaghtigh's cells, as well as the cut-surface size of the MD, were planimetrically

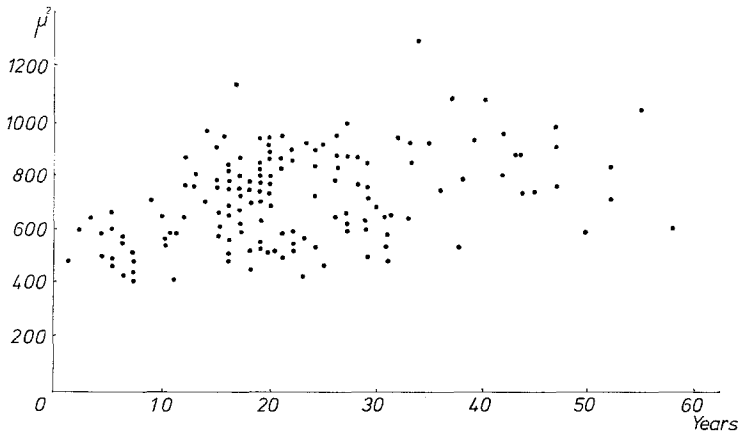

Fig. 1. The size of the juxtaglomerular cell complex (JGC complex) of the controls in relation to age

made. From the JGC complexes observed on 9 to 12 sections of every biopsy, the largest 2 or 3 were selected for measurement and the arithmetic mean for the sizes was obtained as the representative value for the case. This procedure was made to avoid measurements of peripheral cut-surfaces of the juxtaglomerular apparatus. The MD adjacent to the selected JGC complex was also planimetrically measured. When the border of the MD was obscure, or the MD was not discernible, only the JGC complex was measured.

With use of a microscope and a drawing tube, the JGC complex and the adjacent MD were drawn as figures of × 560 magnification, which were then measured by means of a planimeter. Obtained planimetrical units of the drawn figures were multiplied by 20 and converted to square microns of the tissue structure, as described in a previous study (Meyer, 1972).

Statistical Procedure

The JGC complex and MD values for the controls showed the normal distribution ($p<0.05$), but those for the study cases did not. Therfore, not the "t"-test, but the Wilcoxon test was used in comparisons between every study group and the controls, as well as between study groups. The statistical significance in the present study was defined as the level, $p<0.05$.

Results

1. The Difference between Children and Adults in the Size of the Juxtaglomerular Apparatus

In both JGC complex and MD of the controls, the values for children tended to be smaller than those for adults, as shown in Figs. 1 and 2. Concerning the size of the JGC complex and the MD, there seemed to exist a border line between children and adults at the age around 11 years; in the controls, the averages of the JGC complex values for children of 11 years and downward, and for adults above 12 years were $536.5\pm85.5\,\mu^2$ and $742.1\pm162.2\,\mu^2$ (mean$\pm$S.D.); the averages of the MD for the same children and adults were $271.7\pm68.4\,\mu^2$ and $443.1\pm136.2\,\mu^2$. These differences between children and adults for the JGC complex and the MD were statistically significant, respectively ($p<0.001$). Accordingly, the study cases were divided into children (11 years and downward) and adults (above 12 years), and analyzed respectively.

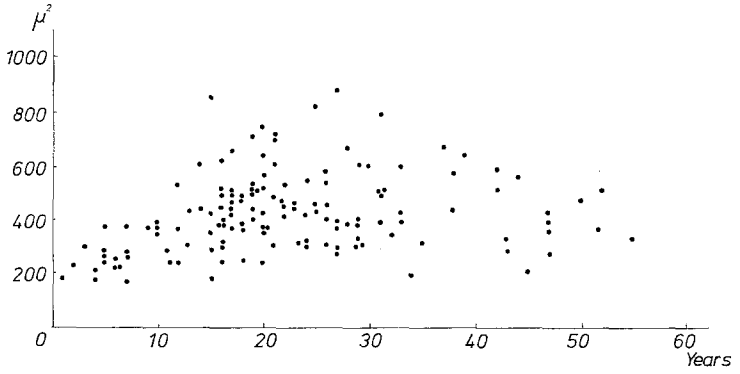

Fig. 2. The size of the macula densa (MD) of the controls in relation to age

2. *Membranoproliferative Glomerulonephritis*

The data concerning the nephrotic syndrome, hypertension, serum creatinine, steroids and diuretics were summarized in Table 1.

The nephrotic syndrome was defined by the association of marked proteinuria (above 3.5 g/day) and hypoproteinaemia (under 6.0 g/dl) or clinical confirmation of generalized oedema. Hypertension in the present study was defined as blood pressures above 150 mmHg systolic, or above 90 mmHg diastolic. Creatinine retention was defined as serum levels above 1.1 mg/dl. The cases of steroid therapy were those which were being treated with steroids at the time of biopsy, or had been treated until a recent date before the time of biopsy. One case of ACTH therapy with steroids and another one of spironolactone administration with steroids were included in the steroid therapy group. Diuretic therapy (furosemide) without steroids was found in 5 cases, which showed no abnormality of sodium or potassium levels in the serum. These 5 cases of diuretic therapy were excluded in the following comparisons in order to simplify the analyses.

The JGC complex values for the nephrotic syndrome group (adult), the non-nephrotic group (adult) and the adult controls were presented in relation to the frequency in Fig. 3. Every difference between the nephrotic group and the non-nephrotic group, between the non-nephrotic group and the controls, and between the nephrotic group and the controls was statistically significant ($p<0.005$, respectively). That is to say, the JGC complex of the nephrotic group was signifi-

Table 1. Study cases of membranoproliferative glomerulonephritis (adult)

		Hypertension			Creatinine retention			Steroids			Diuretics	
		+	−	?	+	−	?	+	−	?	+	−
Nephrotic syndrome	+40	18	21	1	23	11	6	10	22	8	2	38
	−24	14	6	4	10	9	5	7	16	1	3	21
Total	64	32	27	5	33	20	11	17	38	9	5	59

(? = very variable or unavailable data).

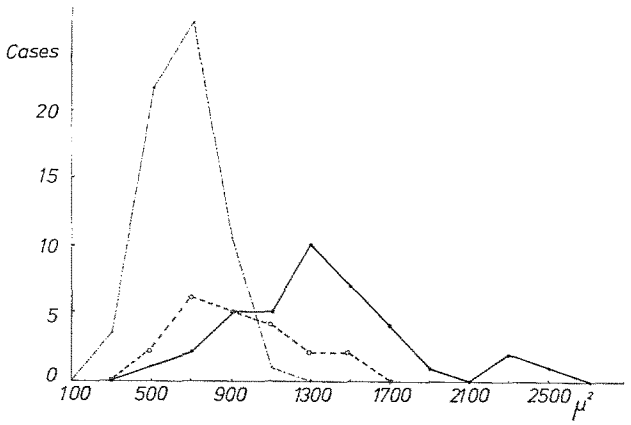

Fig. 3 A–C. Comparison of the size of JGC complex between nephrotic group and non-nephrotic group in membranoproliferative nephritis (adult). (A) •——• Cases with nephrotic syndrome (n 38; median 1380.0; mean 1449.4; S.D. 421.5). (B) o- - - -o Cases without nephrotic syndrome (n 21; median 970.0; mean 1022.3; S.D. 293.8). (C) ·-·-· Adult controls (1/2 scale) (n 126; median 743.3; mean 742.1; S.D. 162.2). A–B difference; significant ($p<0.005$); B–C difference; significant ($p<0.005$); A–C difference; significant ($p<0.005$)

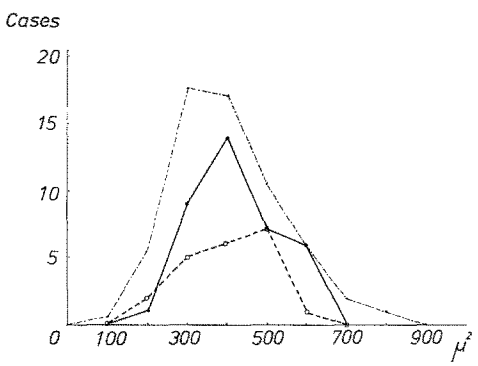

Fig. 4 A–C. Comparison of the size of MD between nephrotic group and non-nephrotic group in membranoproliferative nephritis (adult). (A) •——• Cases with nephrotic syndrome (n 37; median 460.0; mean 461.6; S.D. 102.9). (B) o- - - -o Cases without nephrotic syndrome (n 21; median 440.0; mean 450.7; S.D. 103.6). (C) ·-·-·-· Adult controls (1/2 scale) (n 120; median 428.3; mean 443.1; S.D. 136.2). A–B difference; not significant ($p=0.34$); B–C difference; not significant ($p=0.29$); A–C difference; not significant ($p=0.10$)

cantly larger than that of the non-nephrotic group, which was also significantly larger than the controls.

The MD values for the three groups, the JGC complexes of which were compared above in Fig. 3, are presented in relation to the frequency in Fig. 4. The difference among the three was not significant. In contrast to the significant increase in the size of the JGC complex, there was no enlargement of the MD.

The comparison between the steroid therapy group (adult) and the non-steroid therapy group (adult) was made in the cases showing the nephrotic

Table 2. Comparison of the size of JGC complex between steroid therapy group and non-steroid therapy group in membranoproliferative nephritis (adult)

	n	Median (μ^2)	Mean $\pm$ S.D. (μ^2)	Difference
Steroid therapy cases with nephr. synd.	10	1220.0	1227.6 ± 402.7	significant ($0.025 < p < 0.05$)
Non-steroid cases with nephr. synd.	20	1430.0	1566.9 ± 442.6	
Steroid therapy cases without nephr. synd.	7	1053.4	1018.1 ± 248.6	not significant ($p > 0.05$)
Non-steroid cases without nephr. synd.	13	960.0	1020.2 ± 335.7	

Table 3. Comparison of the size of JGC complex between hypertensive group and non-hypertensive group in membranoproliferative nephritis (adult)

	n	Median (μ^2)	Mean $\pm$ S.D. (μ^2)	Difference
Hypertensive cases with nephr. synd.	17	1380.0	1444.9 ± 428.0	not significant ($p > 0.05$)
Non-hypertensive cases with nephr. synd.	20	1425.0	1461.3 ± 436.0	
Hypertensive cases without nephr. synd.	12	965.0	1016.9 ± 252.9	not significant ($p > 0.05$)
Non-hypertensive cases without nephr. synd.	5	1240.0	1127.3 ± 403.7	
Hypertensive cases with steroids	10	1196.7	1231.3 ± 371.4	not significant ($p > 0.05$)
Non-hypertensive cases with steroids	5	1120.0	1050.0 ± 339.6	
Hypertensive cases without steroids	15	1110.0	1311.5 ± 489.4	not significant ($p > 0.05$)
Non-hypertensive cases without steroids	16	1343.3	1446.2 ± 470.4	

syndrome and in those free of the nephrotic syndrome, respectively (Table 2). The JGC complex of the non-steroid group was significantly larger than that of the steroid group when the nephrotic syndrome was present ($0.025 < p < 0.05$). Furthermore, both of the groups had larger JGC complex than the controls ($p < 0.005$). There was no significant difference between the two groups when the nephrotic syndrome was not present.

The comparison between the hypertensive group and the non-hypertensive group in adults was made under the following conditions; 1) in the nephrotic syndrome; 2) in the absence of the nephrotic syndrome; 3) with steroid therapy; 4) without steroids. The size of the JGC complex showed no significant difference between the two groups under each of the 4 conditions (Table 3).

Table 4. Comparison of the size of JGC complex between creatinine retention group and non-retention group in membranoproliferative nephritis (adult)

	n	Median (μ^2)	Mean $\pm$ S.D. (μ^2)	Difference
Retention cases with nephr. synd.	21	1380.0	1479.5 ± 479.3	not significant ($p > 0.05$)
Non-retention cases with nephr. synd.	11	1480.0	1439.0 ± 360.4	
Retention cases without nephr. synd.	8	1135.0	1122.9 ± 290.2	not significant ($p > 0.05$)
Non-retention cases without nephr. synd.	8	1001.7	1037.0 ± 317.4	
Retention cases with steroids	7	1120.0	1105.7 ± 272.8	not significant ($p > 0.05$)
Non-retention cases with steroids	6	1186.7	1199.4 ± 484.8	
Retention cases without steroids	18	1363.3	1522.3 ± 506.1	significant ($p = 0.047$)
Non-retention cases without steroids	10	1265.0	1189.0 ± 318.2	
Retention cases with hypertension	12	1060.0	1258.6 ± 503.3	not significant ($p > 0.05$)
Non-retention cases with hypertension	11	1320.0	1280.6 ± 383.4	
Retention cases without hypertension	16	1425.0	1536.8 ± 452.2	not significant ($p > 0.05$)
Non-retention cases without hypertension	8	1305.0	1255.0 ± 427.6	

As an index of impaired renal function, serum creatinine levels were used. The comparison between the creatinine retention group and the non-retention group in adults was made under the following conditions; 1) in the nephrotic syndrome; 2) in the absence of the nephrotic syndrome; 3) with steroid therapy; 4) without steroids; 5) in hypertension; 6) in the absence of hypertension. The JGC complex of creatinine retention cases was larger than that of non-retention cases when steroids were not used (Table 4, $p=0.047$). There was no significant difference between the two groups under the other conditions described above (Table 4). There was no case undergoing dialysis in the present study.

There were 5 adult cases which had been treated with furosemide. The sizes of the JGC complex of these were 1060, 1080, 1250, 1340 and 2120 μ^2. The cases of 1250 and 2120 μ^2 had the nephrotic syndrome, which has been shown to be an important factor causing an enlargement of the JGC complex. The number of the cases in the present study was not sufficient to evaluate the influence of diuretics.

There was only one case of child membranoproliferative glomerulonephritis, which showed the nephrotic syndrome without either hypertension or creatinine retention. Steroids were used, but were not effective in this case. The size of the JGC complex was 1000 μ^2 and unusually large as compared with the child controls.

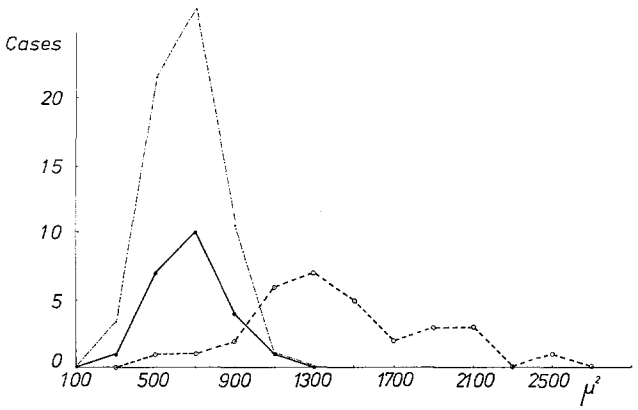

Fig. 5A—C. Comparison of the size of JGC complex between steroid therapy group and non-steroid therapy group in minimal proliferative intercapillary nephritis (MPI) ("minimal changes") in adults. (A) •——• Cases with steroids (one case resistant to steroids was excluded), (n 23; median 770.0; mean 776.3; S.D. 192.3). (B) o- - - - o Cases without steroids (n 31; median 1466.6; mean 1512.2; S.D. 449.3). (C) ·-·-·-· Adult controls (1/2 scale), (n 126; median 743.3; mean 742.1; S.D. 162.2). A–B difference; significant ($p<0.005$); B–C difference; significant ($p<0.005$); A–C difference; not significant ($p=0.16$)

Table 5. Comparison of the size of JGC complex between membranoproliferative nephritis and minimal proliferative intercapillary nephritis (MPI) ("minimal changes") in adults

	n	Median (μ^2)	Mean $\pm$ S.D. (μ^2)	Difference
Nephrotic cases of membranopr. nephritis	38	1380.0	1449.4 ± 421.5	not significant ($p>0.05$)
Non-steroid therapy cases of MPI	31	1466.6	1512.2 ± 449.3	
Steroid therapy cases of membranopr. nephritis	17	1120.0	1141.3 ± 354.5	significant ($p<0.005$)
Steroid therapy cases of MPI	23	770.0	776.3 ± 192.3	

3. Minimal Proliferative Intercapillary Glomerulonephritis (MPI) ("Minimal Changes")

In MPI ("minimal changes"), all of the cases without steroids had the nephrotic syndrome at the time of biopsy. Steroid therapy cases, which had had the nephrotic syndrome before administration of steroids, were in a state of mild proteinuria or complete remission at the time of biopsy, except two cases of the steroid-resistant nephrotic syndrome. The two cases resistant to steroids and another one of ACTH treatment without steroids were excluded in the following comparisons.

In Fig. 5, the sizes of the JGC complex were compared between the adult cases treated with steroids, those without steroids and the adult controls. The

Table 6. Comparison of the size of JGC complex between MPI ("minimal changes") and controls in children

	n	Median (μ^2)	Mean $\pm$ S.D. (μ^2)	Difference
Child controls	23	550.0	536.5 ± 85.5	not significant
MPI with steroids[a]	6	565.0	541.7 ± 133.8	($p > 0.05$)
(MPI without steroids; $n = 1$, the size of JGC complex 1720 μ^2)				

[a] One case resistant to steroids was excluded.

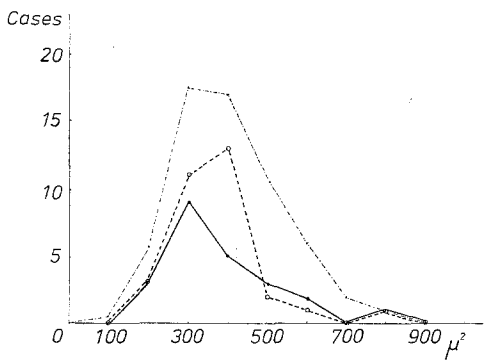

Fig. 6 A–C. Comparison of the size of MD between steroid therapy group and non-steroid therapy group in MPI ("minimal changes") (adult). (A) •——• Cases with steroids (one case resistant to steroids was excluded), (n 23; median 380.0; mean 414.3; S.D. 135.2). (B) o- - -o Cases without steroids (n 31; median 460.0; mean 430.8; S.D. 112.8). (C) ·-·-·-· Adult controls (1/2 scale), (n 120; median 428.3; mean 443.1; S.D. 136.2). A–B difference; not significant ($p=0.21$); B–C difference; not significant ($p=0.37$); A–C difference; not significant ($p=0.11$)

difference between the steroid therapy group and the non-steroid therapy group, as well as the difference between the non-steroid therapy group and the controls, was statistically significant ($p<0.005$, respectively). There was no significant difference between the steroid therapy group and the controls. That is to say, the JGC complex of the non-steroid therapy group was significantly larger than that of the steroid therapy group, which in turn did not differ from the controls. This held true also in children (Table 6).

In Fig. 6, the MD values for the three groups, the JGC complexes of which were compared in Fig. 5, are presented. There was no significant difference among the three. The MD showed no enlargement in contrast to the JGC complex, which exhibited a marked increase in size when steroids were not used.

As aforementioned, there were two cases resistant to steroids, one was 8 and the other 22 years old. The sizes of the JGC complex of the two were 840 and 2010 μ^2. Both values were unusually large as compared with the child and the adult controls respectively. In contrast to the steroid-responsive nephrotic syndrome group, the cases of the steroid-resistant nephrotic syndrome showed an enlargement of the JGC complex even under steroid therapy.

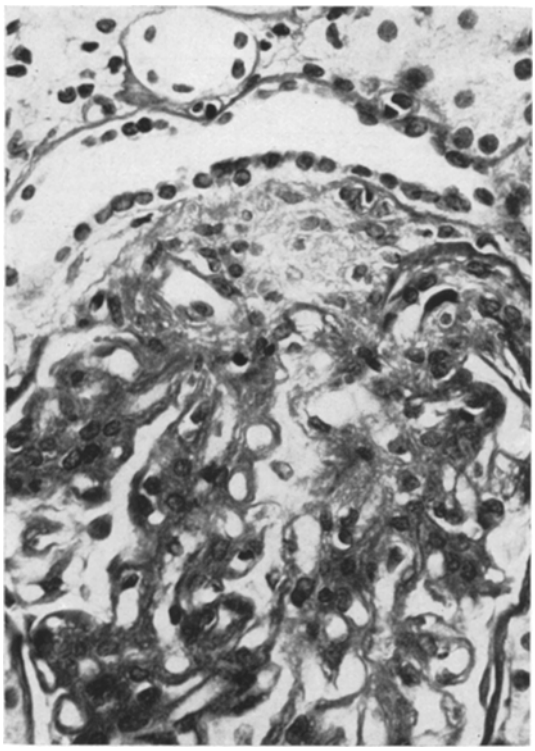

Fig. 7. Moderately enlarged JGC complex with MD of normal size. (70/8/1501. 57 years old man of membranoproliferative glomerulonephritis. PAS. X 440)

In 8 adult cases without steroid therapy, the onset of the disease with the nephrotic syndrome had been 10 to 14 days before the time of biopsy. This time interval from the onset wa the shortest in the present study. The sizes of the JGC complex of the 8 were 520, 720, 1280, 1300, 1467, 1500, 1840 and 2500 μ^2. The median for these values was significantly larger than that of the controls ($p<0.005$). 10 to 14 days' duration of the nephrotic syndrome was shown to be sufficient to bring about an enlargement of the JGC complex.

4. Comparison between Membranoproliferative Glomerulonephritis and MPI ("Minimal Changes")

The sizes of the JGC complex were compared between adult membranoproliferative nephritis showing the nephrotic syndrome and adult MPI without steroid therapy (Table 5). There was no significant difference between the two, both of which had the nephrotic syndrome. On the other hand, in the comparison between membranoproliferative nephritis and MPI, both of which were treated with steroids, the former had larger JGC complex than the latter (Table 5, $p<0.005$). Furthermore, membranoproliferative nephritis with steroid therapy had larger JGC complex than the controls ($p<0.005$), whilst there was no significant difference between MPI treated with steroids and the controls.

5. Histological Findings of the Enlarged Juxtaglomerular Apparatus

Although it was often difficult to distinguish between the epithelioid cells and the Goormaghtigh's cells on the sections stained with PAS, in the enlarged JGC complex, the epithelioid cells tended to be more prominent with an increase in the number of the cells as well as an abundance of cytoplasm (Fig. 7). There was no definite relationship between the size of the JGC complex and that of the MD. A mild enlargement of the MD, which was often observed not only in the study cases but in the controls, was due to an increase in height of the MD cells, basilar vacuolizations and hydropic changes or combinations of these.

Discussion

It has been already reported in a previous study (Meyer, 1972) that the planimetrically measured cut-surface size of the JGC complex consisting of the epithelioid cells and the Goormaghtigh's cells presents a correct index of the activity of the juxtaglomerular apparatus.

The nephrotic syndrome in both membranoproliferative nephritis and MPI ("minimal changes") was accompanied by a significant enlargement of the JGC complex. 10 to 14 days' duration of the nephrotic syndrome was quite sufficient to bring about an enlargement of the JGC complex in MPI. After a clinical resolution of the nephrotic syndrome of MPI by steroid therapy, there was no enlargement of the JGC complex. On the other hand, the steroid-resistant nephrotic syndrome of membranoproliferative nephritis and that of exceptional cases in MPI were associated with an enlargement of the JGC complex even under steroid therapy. The results of the present study indicate that the nephrotic syndrome causes an enlargement of the JGC complex, and this is in agreement with several studies reporting an increase in plasma renin levels in the nephrotic syndrome (Yoshinaga *et al.*, 1963; Veyrat *et al.*, 1964; Imai and Sokabe, 1968; Medina *et al.*, 1974). Decreased plasma volume in the nephrotic syndrome (Eder *et al.*, 1954) is thought to be responsible for enhanced renin release and for the enlargement of the JGC complex.

The suppressive effect of steroids on the size of the JGC complex was very remarkable in the steroid-responsive nephrotic syndrome of MPI, but mild in the steroid-resistant nephrotic syndrome of membranoproliferative nephritis. It is evident from this result that the suppressive effect of steroids on the size of the JGC complex in the nephrotic syndrome is mainly due to the clinical improvement of the nephrotic state. However, judging from the fact that there is a mild suppressive influence of steroids on the size of the JGC complex even in the steroid-resistant nephrotic syndrome (Table 2), it seems likely that a negative feedback on the juxtaglomerular activity, a work of mineralocorticoids by altering sodium balance (Hartroft and Hartroft, 1953; Vander, 1967), participates to some extent in the suppression of the size of the JGC complex.

The influence of hypertension on the size of the JGC complex was not found to be significant in the present study, although a larger group of cases would possibly show a statistically significant tendency (Table 3). The suppressive

effect of hypertension on the size of the JGC complex, if any, seems to be mild. This result is not in accord with the observation by Imai and Sokabe (1968), who emphasized that plasma renin levels are decreased when hypertension is present, even under conditions associated with oedema. In the spontaneously hypertensive rat, the renin-angiotensin system is suppressed (Sokabe, 1965). When hypertension is produced by unilateral ischemia of the kidney, the intact contralateral kidney shows virtual disappearance of the epithelioid cells (Bohle *et al.*, 1953) as well as marked decrease in the degree of granulation of the juxtaglomerular cells (Hartroft, 1957; Tobian *et al.*, 1958). These results cited above are thought to be due to the suppressive effect of hypertension on the juxtaglomerular activity. In the majority of patients with benign essential hypertension, however, the levels of plasma renin do not differ from a normotensive population, whilst only in the remainder, do the levels tend to be lower than normal (Brown *et al.*, 1964; Helmer, 1964). Furthermore, in malignant or accelerated hypertension, plasma renin levels are often markedly increased (Yoshinaga *et al.*, 1963; Helmer, 1964). The influence of hypertension on the juxtaglomerular apparatus may be sometimes paradoxical because of probable renal ischemia due to vascular changes or spasms. The result of the present study, in which the degree of hypertension was quite variable, is similar to the observations by Pitcock and Hartroft (1958), who reported in a study of unselected autopsy cases that the degree of granulation of the juxtaglomerular cells showed no correlation with blood pressure, and is consistent with the result reported by Meyer and his co-workers (1973).

There was a tendency for creatinine retention to be accompanied by an enlargement of the JGC complex. This relationship between creatinine retention and the enlargement of the JGC complex was found to be significant, only in the absence of steroid therapy and was not under the other subdivided conditions, such as under steroid therapy, in the nephrotic syndrome, in the absence of the nephrotic syndrome, in hypertension and in the absence of hypertension. The positive influence of creatinine retention on the size of the JGC complex seems to be mild.

Sodium depletion has an important effect on the renin-angiotensin system (Pitcock and Hartroft, 1958; Aida *et al.*, 1964; de Champlain *et al.*, 1966). In the present study, however, cases showing decreased levels of serum sodium were rare and their number was not sufficient for the study.

In both membranoproliferative nephritis and MPI, the enlargement of the JGC complex was not associated with any enlargement of the MD. Reeves and his co-workers (1963) reported in a study of autopsy cases of liver cirrhosis that there was no correlation between the height of the MD cells and the number of the juxtaglomerular cells, but that increased hydropic changes of the MD were associated with a high number of the juxtaglomerular cells. In the present study, mild hydropic changes or basilar vacuolizations of the MD cells were occasionally observed, but were not always associated with an enlargement of the JGC complex. Some studies, however, report that a positive correlation was found between the degree of granulation of the juxtaglomerular cells and activity of hexose monophosphate shunt enzymes of the MD under several conditions of experimental hypertension (Hess and Pearse, 1959; Fisher, 1961). Accordingly, the functional activity of the MD is probably increased, in spite of no histological enlargement, when the size of the JGC complex is increased. Although controversy continues

as to the relationship between renin release and functions of the MD, many reports indicate that the MD is an intrarenal chemoreceptor and transmits informations to the juxtaglomerular cells, from which renin is released (Vander and Miller, 1964; Thurau and Schnermann, 1965). On the other hand, some studies suggest that the juxtaglomerular cells, as a baroreceptor, respond to a decrease in the perfusion pressure at the terminal end of the vas afferens and release renin (Tobian *et al.*, 1958). In the present study, there was a dissociation between the JGC complex and the MD, concerning the morphological response to the nephrotic syndrome. This dissociation, which is observed not only in the nephrotic syndrome but in several other pathological states causing an enlargement of the JGC complex (Meyer, 1972), may relate to the different ways of stimulation to the juxtaglomerular apparatus.

References

Aida, M., Maebashi, M., Yoshinaga, K., Abe, K., Miwa, I., Watanabe, N.: Changes in plasma renin during sodium depletion in man. Tohoku J. exp. Med. **83**, 11–14 (1964)

Bohle, A., Eichenseher, N., Fischbach, H., Kronenberg, K. H., Wehner, H.: Glomerulonephritis in children and adults. Analysis of 2520 renal biopsies. Proc. 5th int. Cong. Nephrol., Mexico 1972, vol. 1, p. 44–49. Basel: Karger 1974

Bohle, A., Fischbach, H., Wehner, H., Wörz, U., Edel, H. H., Kluthe, R., Scheler, F.: Minimal change lesion with nephrotic syndrome and focal glomerular sclerosis (variations of minimal proliferative intercapillary glomerulonephritis with the nephrotic syndrome). Clin. Nephrol. **2**, 52–58 (1974)

Bohle, A., Kohler, M., Burow, H.: Experimentelle Untersuchungen zur "Endokrinen Niere" (Selye). Virchows Arch. path. Anat. **323**, 1–23 (1953)

Bohle, A., Kohler, M., Tomsche, U.: Über das Verhalten der epitheloiden Zellen der Vasa afferentia einseitig nephrektomierter Ratten bei renaler Hypertonie durch Einkapselung einer Niere. Beitr. path. Anat. **113**, 414–427 (1953)

Brown, J. J., Davies, D. L., Lever, A. F., Robertson, J. I. S.: Variations in plasma renin concentration in several physiological and pathological states. Canad. med. Ass. J. **90**, 201–206 (1964)

Cameron, J. S., Glasgow, E. F., Ogg, C. S., White, R. H. R.: Membranoproliferative glomerulonephritis and persistent hypocomplementaemia. Brit. med. J. 1970 IV, 7–14

Champlain, J. de, Genest, J., Veyrat, R., Boucher, R.: Factors controlling renin in man. Arch. intern. Med. **117**, 355–363 (1966)

Churg, J., Habib, R., White, R. H. R.: Pathology of the nephrotic syndrome in children. A report for the international study of kidney diease in children. Lancet 1970 I, 1299–1302

Eder, H. A., Lauson, H. D., Chinard, F. P., Greif, R. L., Cotzias, G. C., Slyke, D. D. van: A study of the mechanisms of edema formation in patients with the nephrotic syndrome. J. clin. Invest. **33**, 636–656 (1954)

Fisher, E. R.: Correlation of juxtaglomerular granulation, pressor activity, and enzymes of macula densa in experimental hypertension. Lab. Invest. **10**, 707–718 (1961)

Goormaghtigh, N.: Histological changes in the ischemic kidney. With special reference to the juxtaglomerular apparatus. Amer. J. Path. **16**, 409–416 (1940)

Habib, R., Kleinknecht, C., Gubler, M. C., Levy, M.: Idiopathic membranoproliferative glomerulonephritis in children. Report of 105 cases. Clin. Nephrol. **1**, 194–214 (1973)

Habib, R., Michielsen, P., Montera, H. de, Hinglais, N., Galle, P., Hamburger, J.: Clinical, microscopic and electron microscopic data in the nephrotic syndrome of unknown origin. In: Ciba Foundation Symposium on renal biopsy (ed. by G. E. W. Wolstenholme and M. P. Cameron), p. 70. London: Churchill 1961

Hartroft, P. M.: Studies on renal juxtaglomerular cells. III. The effects of experimental renal disease and hypertension in the rat. J. exp. Med. **105**, 501–507 (1957)

Hartroft, P. M., Hartroft, W. S.: Studies on renal juxtaglomerular cells. I. Variations produced by sodium chloride and desoxycorticosterone acetate. J. exp. Med. **97**, 415–427 (1953)

Helmer, O. M.: Renin activity in blood from patients with hypertension. Canad. med. Ass. J. **90**, 221–225 (1964)

Hess, R., Pearse, A. G. E.: The significance of renal glucose-6-phosphate dehydrogenase in experimental hypertension in the rat (a histochemical study). Brit. J. exp. Path. **40**, 243–249 (1959)

Imai, M., Sokabe, H.: Plasma renin and angiotensinogen levels in pathological states associated with oedema. Arch. Dis. Childh. **43**, 475–479 (1968)

Medina, A., Davies, D. L., Brown, J. J., Fraser, R., Lever, A. F., Mallick, N. P., Morton, J. J., Robertson, J. I. S., Tree, M.: A study of the renin-angiotensin system in the nephrotic syndrome. Nephron **12**, 233–240 (1974)

Meyer, D.: Morphometrische Untersuchungen an juxtaglomerulärem Apparat und Macula densa menschlicher Nieren bei verschiedenen Erkrankungen. Versuch einer Korrelation von Struktur und Funktion. Stuttgart: Gustav Fischer 1972

Meyer, D., Jauss, E., Skaane, P.: Quantitative Morphologie des juxtaglomerulären Apparates bei perimembranöser Glomerulonephritis. Verh. dtsch. Ges. Path. **57**, 457 (1973)

Pitcock, J. A., Hartroft, P. M.: The juxtaglomerular cells in man and their relationship to the level of plasma sodium and to the zona glomerulosa of the adrenal cortex. Amer. J. Path. **34**, 863–873 (1958)

Reeves, G., Lowenstein, L. M., Sommers, S. C.: The macula densa and juxtaglomerular body in cirrhosis. Arch. intern. Med. **112**, 708–715 (1963)

Sokabe, H.: Renin-angiotensin system in the spontaneously hypertensive rat. Nature (Lond.) **205**, 90 (1965)

Thurau, K., Schnermann, J.: Die Natriumkonzentration an den Macula densa-Zellen als regulierender Faktor für das Glomerulumfiltrat (Mikropunktionsversuche). Klin. Wschr. **43**, 410–413 (1965)

Tobian, L., Thompson, J., Twedt, R., Janecek, J.: The granulation of juxtaglomerular cells in renal hypertension, desoxycorticosterone and postdesoxycorticosterone hypertension, adrenal regeneration hypertension, and adrenal insufficiency. J. clin. Invest. **37**, 660–671 (1958)

Vander, A. J.: Control of renin release. Physiol Rev. **47**, 359–382 (1967)

Vander, A. J., Miller, R.: Control of renin secretion in the anesthetized dog. Amer. J. Physiol. **207**, 537–546 (1964)

Veyrat, R., de Champlain, J., Boucher, R., Genest, J.: Measurement of human arterial renin activity in some physiological and pathological states. Canad. med. Ass. J. **90**, 215–220 (1964)

West, C. D.: Membranoproliferative hypocomplementemic glomerulonephritis. Nephron **11**, 134–146 (1973)

White, R. H. R., Glasgow, E. F., Mills, R. J.: Clinicopathological study of nephrotic syndrome in childhood. Lancet 1970 I, 1353–1359

Yoshinaga, K., Aida, M., Maebashi, M., Sato, T., Abe, K., Miwa, I.: Assay of renin in peripheral blood. A modification of Helmer's method for the estimation of circulating renin. Tohoku J. exp. Med. **80**, 32–41 (1963)

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