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Schönlein-Henoch Glomerulonephritis

Characteristic Ultrastructural Changes in the Glomerular Basement Membrane and Localisation of Osmiophilic Deposits

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Summary. In glomerulonephritis accompanying the Schönlein-Henoch syndrome (SHS) a characteristic subepithelial basement membrane change is present in 85% of cases. The subepithelial change is a reaction to subepithelial deposits and consists of a garland or dome-like new formation of thin densa lamellae. This change is much more frequent in SHS than in IgA-nephritis or idiopathic glomerulonephritis or any other systemic disease. Furthermore, subepithelial deposits (50% of cases) are nearly as frequent as subendothelial deposits (65%) and more often present than formerly assumed.

Key words: Schönlein-Henoch's disease – Glomerulonephritis – Glomerular basement membrane.

Introduction

The glomerulonephritis (GN) encountered in the Schönlein-Henoch syndrome (SHS) can show any of the morphological types of GN (Zollinger and Mihatsch 1978) including the epimembranous form (Kim et al. 1979).

By light microscopy, Schönlein-Henoch glomerulonephritis (SHG) has no unique features which enable its differentiation from the idiopathic form of the disease. The demonstration of IgA – with and without fibrin(ogen) – does not permit differentiation of SHG from (idiopathic) IgA-nephritis in the absence of clinically established SHS (Nakamoto et al. 1978).

During the past few years, we have noticed a consistent ultrastructural change in the peripheral glomerular basement membrane (Zollinger and Mihatsch 1978) which, we feel, permits a tentative diagnosis of SHG on morphological grounds. In conjunction with clinical findings this change permits the delineation of SHS from idiopathic forms of glomerulonephritis in problem cases. During our systematic search for these basement membrane changes, we also determined

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that subepithelial deposits occurred more frequently in SHG than is generally assumed.

Materials and Methods

32 renal biopsies obtained from cases of clinically assured SHS were examined with light, electron and immunofluorescent microscopy in the usual manner (Zollinger and Mihatsch 1978). As a rule, 2–3 glomeruli from each biopsy were examined with the electron microscope; 954 renal biopsies from cases of glomerulonephritis without clinical indications of SHS served as controls.

Results

General Findings and Diagnosis

Among the 32 cases, diffuse endotheliomesangial GN was found in 11; 7 others also belonged to this group, but showed a pronounced segmental accentuation. In 7 cases, segmental focal accentuated proliferative GN was observed. In 4 cases, membranoproliferative GN, and, in 3 other cases, glomerular minimal change was present. A summary of the light microscopy findings and patient particulars (age, sex, duration of the disease before biopsy) are given in Table 1.

Electron Microscopy

The most impressive feature observed was usually widening of the mesangium with an increase of the matrix and cells (Table 1), except in the cases of glomerular minimal change. Endothelial cells and podocytes always showed signs of activation with swelling and formation of pseudovilli and arcades. The podocytes showed variably severe fusion of foot processes and an increase of osmiophilic material.

Mesangial deposits were present in all 32 cases, in 18 in the mesangial matrix and in 14 along the mesangial basement membrane. Peripheral subendothelial deposits occurred in 21 cases and were associated with deposits along the mesangial basement membrane 16 times. Scanty subepithelial deposits were found in 12 and in 4 further cases they were present only within the subepithelial basement membrane lesion (see below and Table 1). A small number of intramembranous deposits occurred in 9 cases. Typical humps were absent in all cases.

In 4 instances, rupture of the peripheral basement membrane and, in 3 further cases, gross lamellar splitting of the lamina densa were present. In all cases, there was widening of the lamina rara interna which was usually restricted to a few loops and rarely accompanied by a de novo formation of a thin densa lamella. Mesangial interposition was present in 11 of the 32 cases (Table 1).

Virus-induced endothelial tubules were found 5 times. Occasionally, large and small strongly osmiophilic granules surrounded by a delicate membrane and having a diameter of 40–60 nm were seen subepithelially.

Arterioles were evaluated by electron microscopy in 21 of the 32 cases. In 17 they were unchanged; in 2, mild arteriolitis without fibrinoid necroses was encountered and, in a further case, severe swelling of the endothelium was observed. In only one instance (case 25) was severe arteriolitis with fibrinoid necroses and arteriitis of the hypersensitivity-angitis type noted.

Subepithelial Basement Membrane Changes

Three types of subepithelial basement membrane lesions in SHS can be distinguished (see Table 1, 2, Fig. 1).

Type A. Garland-shaped, severe widening of the lamina rara externa always associated with de novo formation of a thin densa lamella (Fig. 2, 3, 4a).

Extremely fine granules with an average diameter of 25 nm and/or osmiophilic deposits or deposit remnants, occurred between the original lamina densa – which was usually thinned – and the newly formed densa lamella. The podocytes overlying this basememt membrane lesion showed a marked increase of the fibrillar osmiophilic material and complete fusion of the foot processes.

Type B. Changes as in type A and, in addition, identical lesions in the lamina rara interna (Fig. 4b).

Type C. Dome-shaped processes of the lamina rara externa, which may also contain osmiophilic deposits or remnants thereof (Fig. 3, 4c,d). In contrast to the spikes encountered in epimembranous GN, the processes were considerably larger and much less frequent.

The frequency, extent and type of the lesions are given in Table 1 and 2. We have designated the changes occurring in type A and B as long (l), if they encompass at least half of a peripheral loop; the others are designated as short (s).

Short type A lesion was observed in 11 cases, in which osmiophilic deposits were present in 5. Long type A lesion was observed in 3 cases, all of which evidenced extensive deposits. Short type B lesion was found twice, both times with extensive deposits and long type B lesion 4 times, always associated with deposits. Type C lesion occurred 7 times without and 3 times with deposits and it was associated with types A and B 6 times.

In 5 of the 32 cases ($\sim$15%) no subepithelial basement membrane lesion could be found.

Control Group. Cases of GN without clinical evidence of SHS.

Epimembranous GN and glomerulonephritic mixed forms (membranoproliferative and epimembranous GN) were excluded, since they are, depending on the stage of development, invariably accompanied by a subepithelial basement membrane lesion.

Table 1. Summary of patient particulars, electron- and light microscopy

Case No	Age (yrs) sex	Biopsy in ... weeks after disease onset	Type and extent of basement membrane change	Virus-like particles	Mesangial enlargement	Mesangial interposition
Diffuse endothelio-mesangial GN						
1	11 ♂	20	C±	∅	+	∅
2	10 ♀	52	A_s+	∅	++	∅
3	$4^1/_2$ ♀	6	A_l, D++	g+, t++	++	∅
4	59 ♀	4	C+	g+	++	∅
5	6 ♂	8	∅	t+	+	∅
6	4 ♀	28	A_s+	t+	++	∅
7	7 ♂	12	A_l, D+++, C+	g+, t++	++	∅
8	$4^1/_2$ ♀	10	A_s+	∅	+	∅
9	17 ♀	16	A_s, D++	∅	+++	∅
10	7 ♀	40	A_s+	∅	+	∅
11	9 ♀	6	∅	∅	++	∅
Diffuse endothelio-mesangial GN with segmental accentuation						
12	10 ♀	32	B_s, D++, D, D++	g+	++	∅
13	8 ♂	8	A_l, D+++, C, D+++	g+	+++	+
14	5 ♂	4	B_l, D++, C, D++	∅	++	+
15	$7^1/_2$ ♂	9	C, D++	t+	++	++
16	13 ♀	50	A_s, D+	∅	++	+
17	13 ♂	8	A_s+	∅	++	∅
18	43 ♂	208	A_s+, D+	∅	++	+
Focal-segmental GN						
19	6 ♂	16	B_l, D+++	g+	±	∅
20	10 ♀	16	∅	∅	+	∅
21	7 ♂	12	C+	∅	++	∅
22	8 ♂	36	B_l, D+, C+	∅	+++	++
23	8 ♂	156	A_s, D+	g+	+++	+
24	12 ♀	3	A_s, D++	∅	±	∅
25	7 ♂	7	B_l, D+	∅	++	∅
Membrano-proliferative GN						
26	61 ♀	3	∅	∅	++	+
27	8/12 ♀	14	C, D++	∅	+++	++
28	9 ♀	?	B_s, D++	∅	+	+
29	51 ♂	204	C, D+	g+	++	+
Glomerular minimal change						
30	9 ♀	24	C+	∅	±	∅
31	$5^1/_2$ ♂	36	∅	∅	±	∅
32	9 ♀	20	A_s+, C+	g+, t+	±	∅

A/B/C = Types of basement membrane changes, s. Fig. 1
s/l = short/long, s. text
n_c = number of glomeruli with crescents
n_h = number of obsolescent glomeruli
n_t = total number of glomeruli
g = granular
t = tubules in endothelium

Deposits					Light microscopy $n_c/n_h/n_t$
Subendothelial	Subepithial	Mesangial		Intramembranous	
		along BM	Matrix		
+	∅	AM+++	+	∅	∅ c, ∅ h/25
∅	∅	AM++	∅	∅	1 c, 1 h/9
+	±	∅	∅	∅	1 c, ∅ h/42
∅	∅	AM+	±	±	∅ c, ∅ h/4
+	∅	∅	∅	∅	∅ c, ∅ h/44
∅	∅	∅	∅	∅	2 c, ∅ h/38
∅	+	AM++	+	∅	∅ c, ∅ h/29
+	∅	AM+	±	∅	∅ c, ∅ h/13
+	±	AM++	+	∅	1 c, 1 h/26
∅	∅	∅	∅	±	∅ c, ∅ h/37
+	∅	∅	∅	∅	∅ c, 2 h/18
+	+	AM++	+	∅	2 c, ∅ h/10
++	+	∅	+	∅	∅ c, 1 h/38
+	∅	AM+++	+	∅	1 c, ∅ h/26
++	+	AM+	±	+	4 c, 1 h/40
+	±	AM+	++	+	∅ c, ∅ h/22
∅	∅	AM+	±	∅	∅ c, ∅ h/11
++	+	AM+	∅	±	∅ c, 2 h/11
+	++	∅	+	+	1 c, 2 h/16
++	∅	AM++	+	+	6 c, ∅ h/27
∅	∅	∅	∅	∅	7 c, 2 h/11
++	+	AM+	∅	∅	1 c, ∅ h/4
∅	+	AM++	+++	+	∅ c, 3 h/10
+++	++	AM+++	∅	∅	∅ c, ∅ h/4
∅	±	AM+	∅	∅	3 c, 3 h/5
++	∅	AM++	++	∅	2 c, ∅ h/15
+	+	AM+++	±	∅	1 c, ∅ h/15
+	+	AM++	+	±	∅ c, 4 h/4
+	±	AM++	∅	∅	∅ c, 1 h/14
∅	∅	∅	∅	∅	∅ c, ∅ h/30
+	∅	∅	∅	∅	∅ c, ∅ h/3
∅	∅	AM+	+	∅	∅ c, ∅ h/8

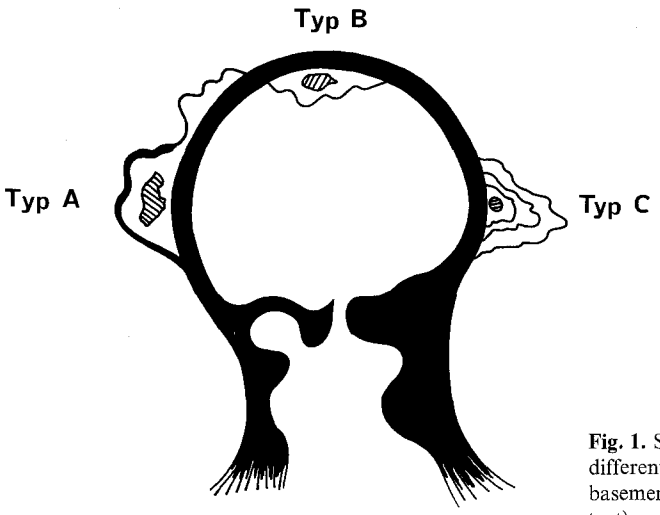

Fig. 1. Schematic presentation of the different types of subepithelial basement membrane changes (see text)

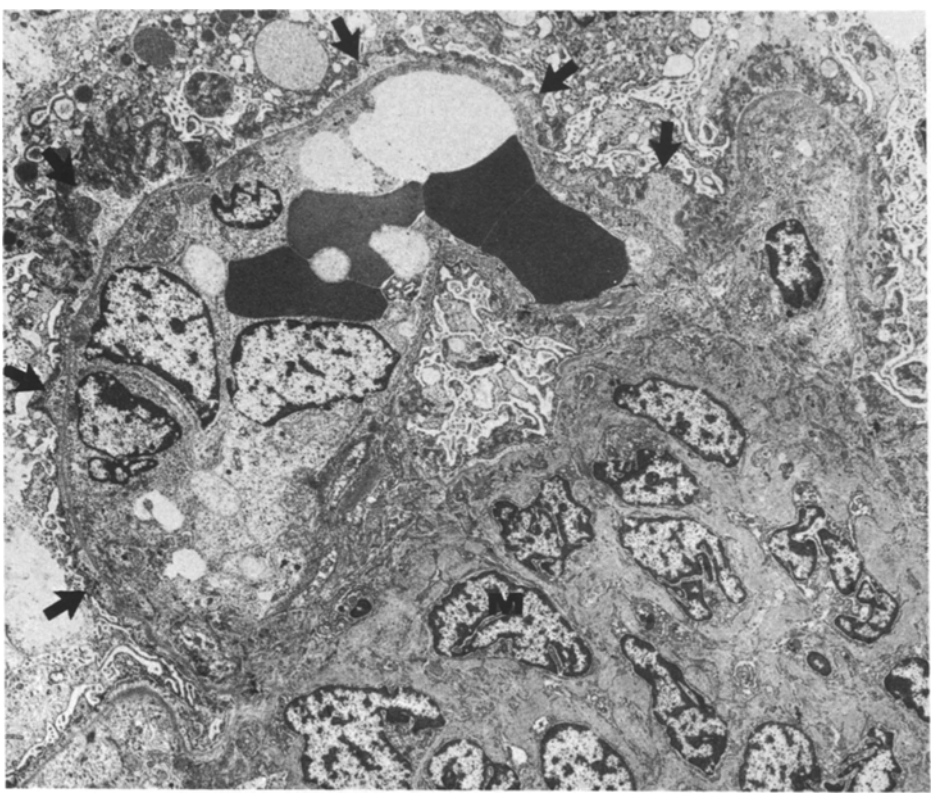

Fig. 2. Glomerular loop and adjacent mesangium (*M*) with pronounced matrix and cell increase. Extensive garland-like subepithelial basement membrane change (→). EM (×3,900)

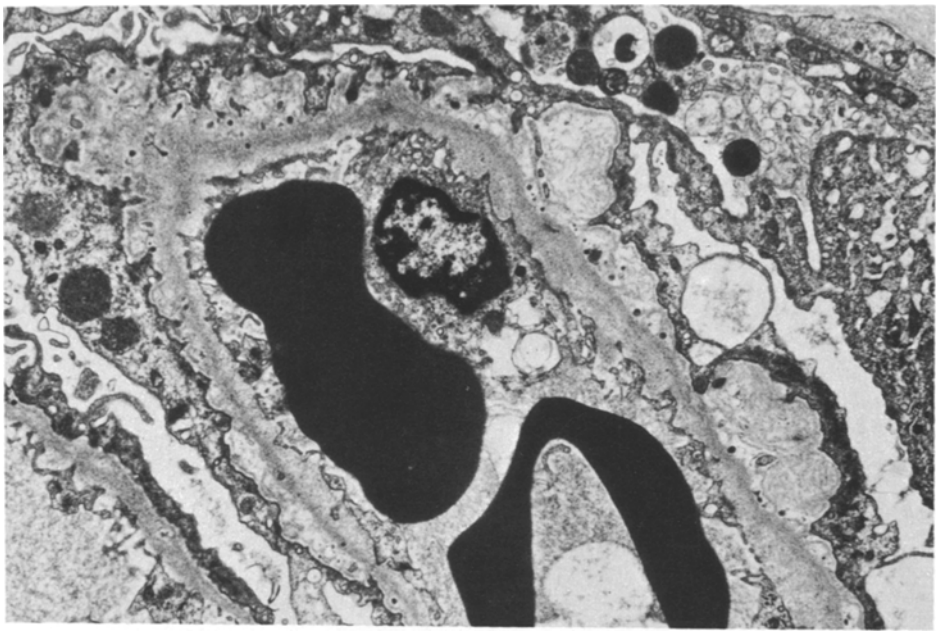

Fig. 3. Glomerular loop with extensive garland and dome-like subepithelial basement membrane changes. Focal thinning of lamina densa. EM (×9,000)

Among the 954 cases of GN examined with electron microscopy, we found a total of 46 (4.8%) cases with type A, B or C subepithelial basement membrane changes (Table 2). Types A and B predominated in the control as in the SHS group. Deposits were found in the basement membrane lesion in more than half of the cases.

Among the 46 cases, we encountered 2 with systemic lupus erythematosis (6% of all cases of systemic lupus erythematosis examined with electron microscopy), 1 with the Goodpasture syndrome and 5 with IgA-nephritis (10.8% of all electron microscopically examined cases of IgA-nephritis).

The A, B and C types of basement membrane lesion occur in 85% of our SHS cases which is significantly more frequent than in the control group (4.8%; $p < 0.05$, χ^2-test).

Immunofluorescence

The antigens studied were found somewhat more frequently in cases of SHG than in those of the control group (Table 3). With respect to intrarenal antigen distribution, we found a slight predominance of focal and segmental glomerular localisation in the control group. In the cases of SHG the intraglomerular deposition of antigens was chiefly peripheral and mesangial, while in the control group pure peripheral occurrence predominated.

Table 2. Type of basement membrane change and glomerulonephritis in Schönlein-Henoch Syndrome and control cases

Schönlein-Henoch Syndrome			Control cases: No indication of SHS		
Type of basement membrane change	n	Type of glomerulonephritis (GN)	n	Type of basement membrane change	n
5 D*+, 6 D− / A – short (n=11)	18	Endothelio-mesangial GN	9	A – short (n=18) / D+	11
				D−	7
3 D+, 0 D− / A – long (n=)	4	Membranoproliferative GN	9	A – long (n=6) / D+	4
				D−	2
2 D+, 0 D− / B – short (n=2)	–	Extracapillary accentuated GN	1	B – short (n=17) / D+	
				D−	
4 D+, 0 D− / B – long (n=4)	7	Segmental/focal proliferative GN	16	B – long (n=3) / D+	2
				D−	1
3 D+, 4 D− / C (n=7)	3	Glomerular minimal change	6	C (N=2) / D+	1
				D−	1
C+A+B (n=6)				C+A+B (n=4)	
Total positive (n=27)				Total positive (n=46)	
Total negative (n=5)				Total negative (n=908)	

* D+/− =Osmiophilic deposits present/absent

Table 3. Immunofluorescence findings

		Schönlein-Henoch Syndrome n=22					Control cases n=25				
	Antigens	G	M	A	C_3	Fi	G	M	A	C_3	Fi
	Cases tested	22	22	22	22	22	25	25	25	25	25
	positive	16	13	16	15	13	16	17	12	18	5
Distribution in the kidney	diffuse	14	11	15	15	12	12	13	10	14	5
	focal	2	2	1	0	1	4	4	2	4	0
	global	13	9	14	12	17	11	10	12	10	5
	segmental	3	4	2	3	1	5	7	0	8	0
	peripheral	5	4	2	4	7	12	13	7	8	4
	peripheral + mesangial	10	5	10	7	5	2	4	2	8	1
	mesangial	1	4	4	4	1	2	0	3	2	0

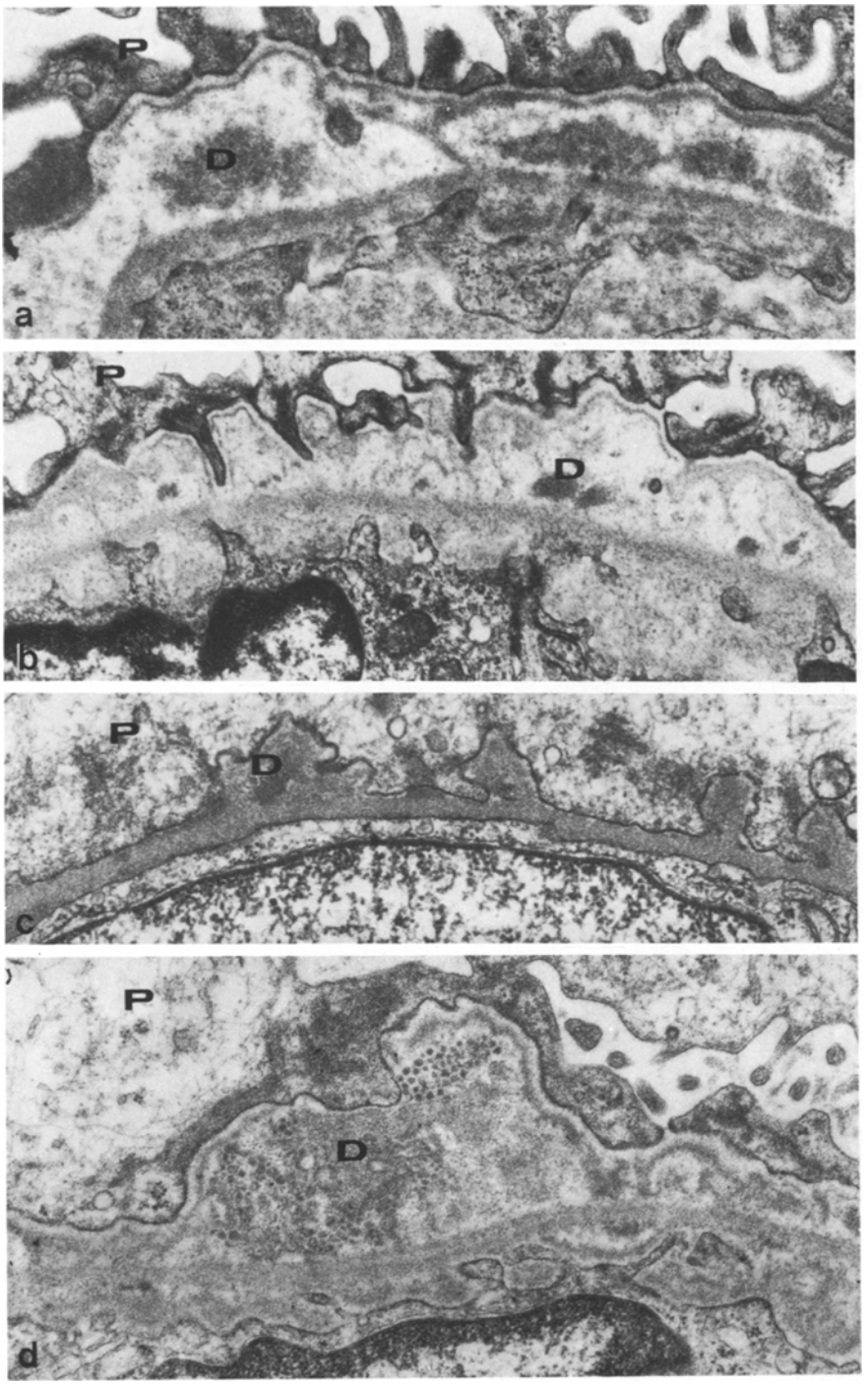

Fig. 4a–d. Subepithelial basement membrane changes (*BM*): *P*=Podocyte, *D*=Osmiophilic deposit. **a** Garland-like subepithelial BM change (type A). Deposits are surrounded by a translucent zone and a newly formed densa lamella which is covered by podocytes. EM (×33,500). **b** Garland-like subepithelial BM change. Similar changes are present in the subendothelial zone (type B). EM (×19,500). **c** Small dome-like subepithelial protrusions (type C). EM (×29,000). **d** Large dome-like subepithelial change (type C). A newly formed densa lamella covers a deposit with numerous round virus-like particles. EM (×26,000)

Discussion

Light microscopic, immunofluorescent and general electron microscopic findings and the frequency distribution of GN in SHS agree with corresponding findings in the literature (Zollinger and Mihatsch 1978, for lit). In our series of biopsies, membranoproliferative GN in SHS was the only form encountered with a somewhat higher frequency than the normal one of about 1%. This may be attributable to factors involved in selection of patients for renal biopsy.

The subepithelial basement membrane lesions described in this paper in SHG (type A, B, C) have, certainly, been mentioned and even presented visually, but have not hitherto received direct attention (Urizar et al. 1968, Brun et al. 1971, Heaton et al. 1977).

From statistical evaluation these subepithelial basement membrane lesions are apparently highly characteristic for SHG. They are encountered more frequently in SHS than in other systemic diseases, in IgA-nephritis (Clarkson et al. 1977) or in other GN without SHS involvement, excluding epimembranous GN and glomerulonephritic mixed forms. Therefore, we feel that the demonstration of this lesion justifies the tentative diagnosis of SHS and thus contributes to a definite classification of GN in problem cases with an uncertain clinical history.

It is not surprising that the basement membrane lesion is not found in every case since it is often present in only a few glomerular loops and can easily be overlooked as the result of sampling. However we cannot exclude the possibility that, in the control series, cases of SHS may be included which were overlooked clinically as a result of discrete and transient symptoms and vague case histories.

Pathogenetically, the subepithelial basement membrane lesions can be interpreted as a reaction to the subepithelial deposits. This view is supported by the frequent occurrence of deposits – or their remnants – in the centre of the lesion. These deposits must, however, be qualitatively different from humps which are not associated with membrane responses of this kind. Moreover, humps were not seen in our series. Deposits which are illustrated in the literature as humps in SHG are atypical (Urizar et al. 1978, Heaton et al. 1977).

Contrary to current thinking it must be realized that subepithelial deposits are by no means rare (Urizar et al. 1968, Urizar et al. 1978, Brun et al. 1971, Sinniah et al. 1978, Kim et al. 1979). We have found mesangial deposits in all of our cases (Heaton et al. 1977: in 68.4%, $n=19$), subendothelial deposits in 65% (Heaton et al. 1977: in 47.4%), subepithelial deposits in 50% (Heaton et al. 1977: in 15.8%) and intramembranous deposits in 28% of our cases. We suggest that the subepithelial basement membrane changes described herein arise as a reaction to deposits and that in these circumstances subepithelial deposits are at least as frequent as those occurring subendothelially. It must be conceded however, that subepithelial deposits are, as a rule, very small and more scarce, so that they can be easily overlooked. Immunofluorescence findings do not permit clear-cut conclusions regarding the immunoglobulin composition of the subepithelial deposits since practically all immunoglobulins and complement (C_3) occur with the same frequency in the glomeruli.

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