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Extramembranous Deposits and "Membranous" Glomerulonephritis

Their Fine Structure, Development, and Correlation

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Summary. In 15 renal puncture biopsies from 14 patients, electron microscopy revealed extramembranous deposits (EMD) in various developmental stages (or their residues) in glomerular capillaries. Florid EMD exhibited a regular granular substructure as well as a typical localization within the subpodocytal space. Ultrastructurally, a gradual regression of EMD and their incorporation into the basement membrane could be observed. Early florid EMD were found in acute glomerulonephritis or in the nephrotic syndrome persisting for several months, with only discrete to absent "membranous" changes with light microscopy. Late stages of EMD with predominantly degenerative changes of glomerular basement membranes and apparent "membranous" thickening in light microscopy, on the other hand, were characteristic of the nephrotic syndrome lasting for several years. At early stages of EMD, long-lasting remission up to clinical healing were observed in a half of the cases studied, whereas at a late "membranous" stage long-lasting remission took place only once in six cases.

Extramembranous (peri-or epimembranous, subepithelial) deposits (*EMD*) are minute, dense, granular foci, disseminated in more or less dense clusters overall the external surface of glomerular capillaries. The presence of EMD can be reliably proved, and their internal structure revealed, only by electron microscopy. EMD have been successively found to be associated with various renal lesions, of which in man the most important are acute glomerulonephritis, chronic "membranous" glomerulonephritis, and disseminated lupus erythematosus (Spargo and Arnold, 1960; Galle *et al.*, 1962; Huhn *et al.*, 1962), and in animals, experimental immune complex disease and certain spontaneous glomerulopathies (Movat *et al.*, 1961; Moppert and Fresen, 1967; Dixon *et al.*, 1971; Oldstone and Dixon, 1971). The present study, based on 15 renal biopsies with positive finding of EMD, discusses the discrete, but characteristic, manifestations of the development and the regression of EMD, certain clinico-morphological aspects, and problems of their reversibility.

Material and Methods

Within the period 1967–1971, EMD were discerned by electron microscopy in 15 puncture renal biopsies performed in 14 patients. The tissue samples were fixed in 2 per cent isotonic OsO_4 and embedded in Vestopal W or Epon 812. Sections within the silver interference area, cut with LOB knives on a microtome Tesla BS 478, were contrasted with uranyl acetate, partially also with lead acetate, and examined at 60 kV in a microscope Tesla BS 242 D.

Semithin sections (0.5–1.0 μm), stained with toluidine blue and those about 0.25 μm, impregnated with hexamin-silver (Movat, 1961) were examined microscopically. For routine examination, formol-fixed, paraffin-embedded sections were stained with H.-E., PAS, blue trichrome, elastica-van Gieson stain and toluidine blue.

Results

Primely, characteristic glomerular lesions are described whose extent and stage are summarized in Table 1.

Table 1

Name, Sex, age at biopsy	Histology			Electron microscopy			Clinical signs				
	Capill. wall thickening	Bas. membr. thickening (PAS)	Endocapill. proliferation	EMD granular (florid)	EMD regressive	Lamina densa changes	Onset A = acute I = insidious	Duration before biopsy (mo.)	Proteinuria at biopsy (g/24 h)	Follow up after biopsy (mo.)	Proteinuria, last record (g/24 h)
1) J. S., ♀, 46	++	++	0	0	++	++	I	30	1.5–8	3	4.2
2) K. R., ♂, 44	++	++	0	0	++	++	I	23	10	10	17.1
3) V. V., ♀, 32	++	++	0	0	++	++	I(?)	120	11	6	10.7
4) A. K., ♂, 40	++	++	0	+–	++	++	I	34	8–13	27	10.8
5) B. M., ♂, 16	++	++	0	+	++	++	A	120	2.2	15	5.8
6) I. Š., ♀, 19	++	+	0	+	++	++	I	30	6.6	15	0.8
7) E. C., ♂, 49	+	+	+–	++	+	+	I	4	10–12	7	6.7
8) M. V., ♂, 17	+	+–	0	++	+	+	I	9 (18)	10–12	27	13.1
9) I. C., ♀, 47	+	+–	+	++	+–	+–	I	6	4.7	4	6.6
10) J. P., ♂, 27	+	0	0	++	+	+–	I	21/2	8	19	10
11) F. S., ♂, 51	+	0	0	++	+	+	A	4	2.6–3.5	8	1
12) V. K., ♂, 31	+–	+–	+	++	+–	+–	A	5	12–14	52	2.1
13) M. S., ♂, 11	+–	0	+–	++	+–	+–	A	3	2.4–4.5	27	0
2nd biopsy	0	0	0	+–	+	+–					
14) M. P., ♂, 13	+–	0	+–	+–	+	+–	A	3	2.4	12	0

Degree of involvement: ++ severe, evident at first sight, + moderate to discrete, 0 absent.

Optical microscopy revealed classical "membranous" glomerulonephritis in the patients No. 1–6: both the capillary walls (H.E.) and the basement membranes (PAS, toluidine blue in semithin sections) were severely involved while endocapillary proliferation was absent. The basement membranes exhibited homogeneous as well as "felty" thickening. In semithin sections, reticular patterns and bulging external contours of the capillary walls and mesangium were apparent. In Ag-impregnated sections, the original basement membranes remained discernible as thin brown-black lines at the inner capillary contour, while the outer surface displayed delicate networks and guirlands of minute dark trabecular projections.

In the cases No. 7–14, the capillary thickening appeared moderate to minimal. The basement membranes (PAS) were slightly thickened or normal, even so in the cases No. 8–11 with apparent moderate "membranous" changes in H.E.

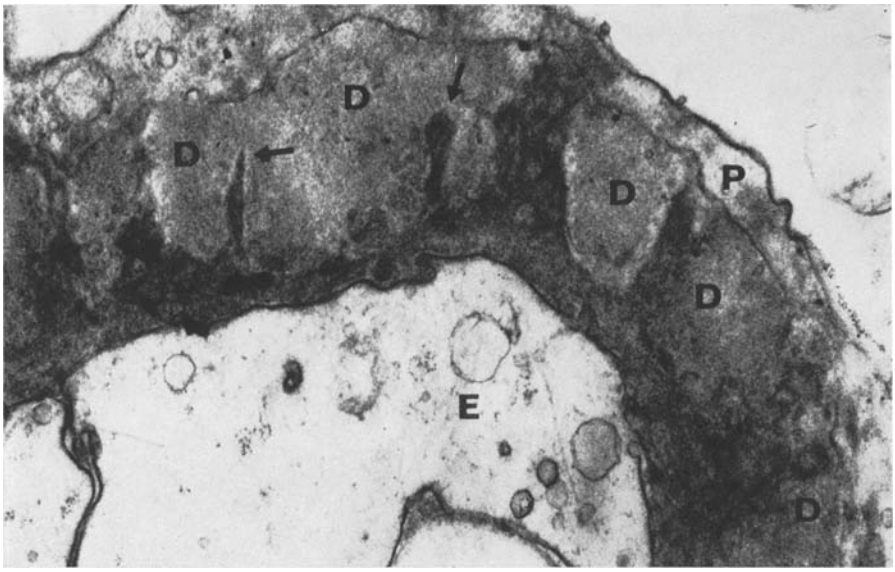

Fig. 1. Case 8. Dense dissemination of deposits (*D*) over outer surface of the capillary basement membrane. Slender projections (*arrows*) of basement membrane material between adjacent deposits. Diffuse fusion of foot processes (*P*). Swelling of endothelial cell (*E*). ×26100

and trichrome. Endocapillary proliferation (5 times) was discrete and in the cases No. 7, 12 and 14, it was accompanied by slight leukostasis. In toluidin-blue-stained semithin sections, the external contours of basement membranes were seeded by minute dark-blue hemisphaeroid protrusions, corresponding to the florid EMD; less afflicted capillary segments were apparent even in those biopsies (No. 7–11) where dense regular dissemination preponderated. In the cases No. 12 and 13 (first biopsy), considerable areas of capillary tuft were free of EMD and individual granules of EMD were larger and less regular in size. In the two last biopsies (bottom of Table 1), no typical dark protrusions were found.—In Ag-impregnated semithin sections, the consistent rows of faintly impregnated EMD were typically interposed by "ladders" of delicate, acute, brown-black perpendicular projections. In the two last biopsies, only minute irregular extrinsic focal thickenings and trabecular protrusions were recorded while the mesangium showed a moderate non-lobular expansion.

Electron Microscopy. The most conspicuous features of glomerules were the EMD proper and the various changes of the capillary basement membranes and podocytes. *Homogeneous granular EMD* (Figs. 1, 2 on the left) appeared in the form of discoid and hemisphaeroid foci (diameter about 0.5–1.5 μm, exceptionally up to 3–4 μm), adherent to the external contour of lamina densa and consisting of fine granular precipitate. The latter exhibited a considerable density, which however, also depended on the fixing and contrasting methods used (increased density after Pb). The bodies of EMD exhibited signs of local expansion into the adjacent lamina densa, which was pitted and thinned down to 0.15 μm at the

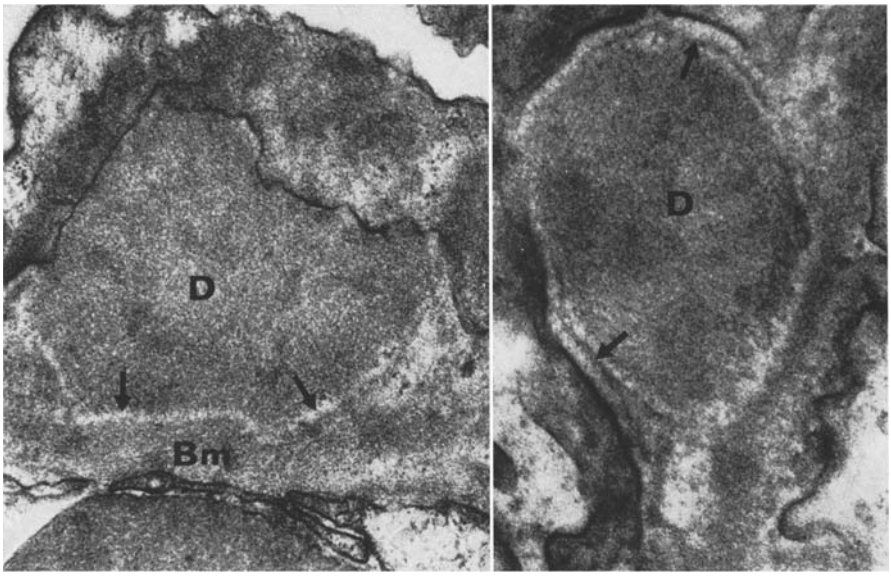

Fig. 2. At left: Case 10. Detail of a florid deposit (*D*) consisting of dense granular substance, bordered by a narrow translucent rim (*arrows*) and "pitting" the adjacent basement membrane (*Bm*). ×39800. At right: Case 5. Lateral faces of the deposit (*D*) are contoured by thin projections of basement membrane material (*arrows*). ×43700

bottom of an EMD. In the periphery of most EMD, a thin translucent slit was apparent (200–300 Å wide) whereas the lamina rara externa was always absent in these areas. These "florid" EMD were primely seen in cases with microscopically discrete or minimal thickening of capillary walls (No. 7–13), whereas in those of a classical "membranous" lesion (No. 1–6) they were sparse, less conspicuous, with secondary changes predominant. In three cases (No. 1, 2, 3) the EMD were not discernible in the ultrastructure any more.—*Regressive changes in EMD and basement membranes*—of a moderate degree at least—were seen in all bioptic specimens: their grade corresponded to that of the "membranous changes" as revealed by optical microscopy.—The most discrete changes in the lamina densa were slender processes ("spicules"), delimiting both lateral faces of the EMD. Their width lay between 400–2500 Å, and length, between 0.3–1.0 μm. Such spicules were most conspicuous in the areas of dense dissemination of EMD (Fig. 2, on the right). By thickening, extension, and fusion of lateral processes of the membranoid substance the EMD successively became "embraced" by and incorporated into the lamina densa (Fig. 3). The bridges thus produced from the lamina densa had a width of 250–1000 Å, and on their surface the lamina rara externa reappeared, focally at least. An incorporation of EMD was mostly accompanied by changes in their substructure: the granular substance assumed then a coarse irregular pattern and exhibited a decrease in density with translucent cavities and fissures, osmiophilic (lipid?) globules and non-periodic filaments. Even at this stage of incorporation the contours of the original EMD remained

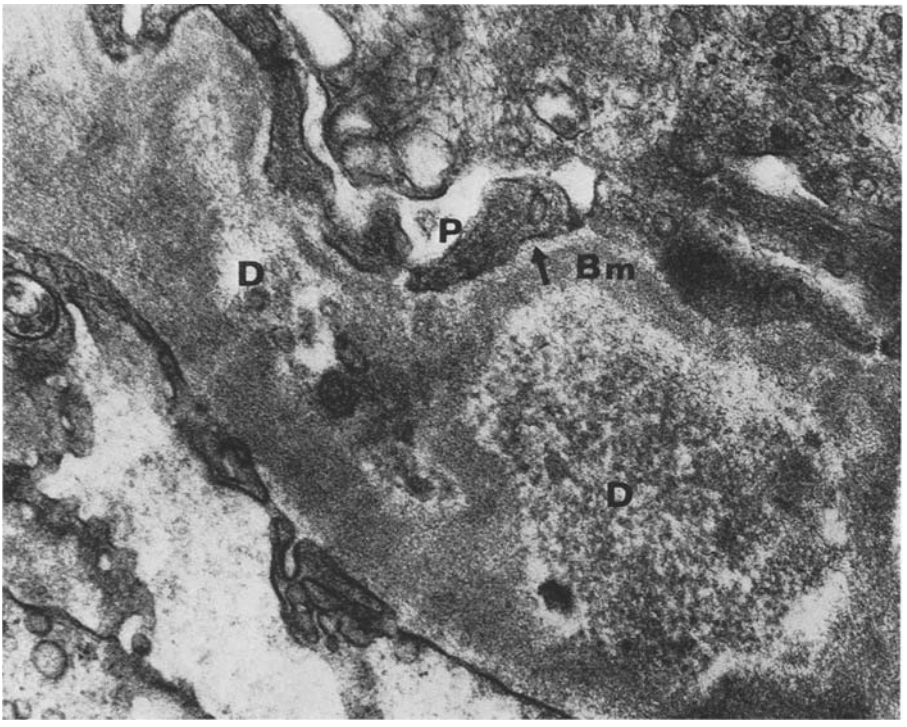

Fig. 3. Case 5. Coarse granular structure and apparent dense bodies and translucent cavities within the deposits (*D*) which are bridged by a layer of basement membrane material (*Bm*). Reconstruction of lamina rara externa (*arrow*) and foot processes (*P*). ×41500

partially preserved; mostly, however, their margins merged with the adjacent basement-membrane-material. The resulting formation was a strongly thickened basement membrane, in which the original lamina densa occupied only the internal layers—about $^1/_4$–$^1/_3$ of the total thickeness, whereas the external layers consisted of aggregated, disintegrated deposits, interspersed with patches and strips of membranoid substance. The external surface of this area of débris was always distinctly uneven, "bumpy". In certain localities, especially in the cases No. 1 and 6, the thickened basement membrane assumed a fairly homogeneous structure, and EMD were not discernible any more (Fig. 4). The irregularity of the outer contours, however, revealed even here the actual origin of the lesion.—A good correlation was found between the degree of microscopical and ultrastructural capillary changes. An ultrastructural thickening of the basement membrane, amounting to about 1.5–2 μm, was appraised as severe at the first glance in optical microscopy (PAS, cases No. 1–6), whereas that amounting to 0.8–1 μm was microscopically judged as discrete (No. 7–10). A thickening of about 0.5–0.7 μm already was beyond reliable optical recognition in routine paraffin sections. Even when discrete microscopical thickening was recorded, focal protrusions thicker than 1 μm were apparent in the ultrastructure. On the

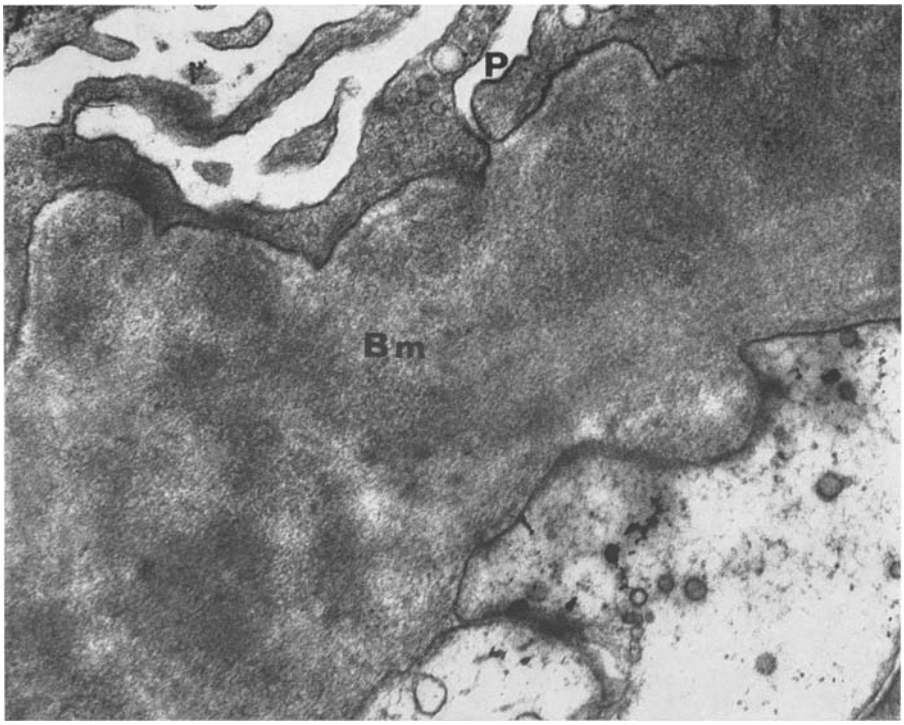

Fig. 4. Case 1. Advanced membranous transformation without apparent deposits. Characteristically uneven outer surface of the basement membrane (*Bm*). Reconstruction of lamina rara externa and foot processes (*P*). ×33200

other hand, short segments of a normal basement membrane were observed even in the presence of massive "membranous" lesions (No. 1, 2, 5). In all instances, such focal irregularities occupied too short segments (fraction of μm) as to be discernible by optical microscopy. Apart from these discrete irregularities, the extent, whether of florid EMD or of secondary changes, was practically diffuse in the first 11 cases. In the remaining 3, larger areas of capillaries (even whole loops) remained free. In the case No. 14, most capillaries were intact.—The main change in *podocytes* was a fusion of foot processes, ubiquitous and diffuse in the area of florid granular EMD. The adjacent cytoplasmic areas displayed increased density. In biopsies with advanced incorporation of EMD and secondary changes in lamina densa the foot processes were focally preserved (regenerated ?), partially polymorphous. The podocytal cytoplasm exhibited multiple vesicles and vacuoles of the endoplasmic reticulum, mainly of the smooth type, and the Golgi zones were extended. In the Bowman's space, microvillous projections, partly numerous, were apparent. In glomerular areas free from EMD (No. 12–14) the podocytes exhibited only little damage. *Endothelial cells* showed focal swelling and hyperplasia of microvillous projections; nevertheless, segments with normal fenestration were present even in areas of massive EMD and membranous second-

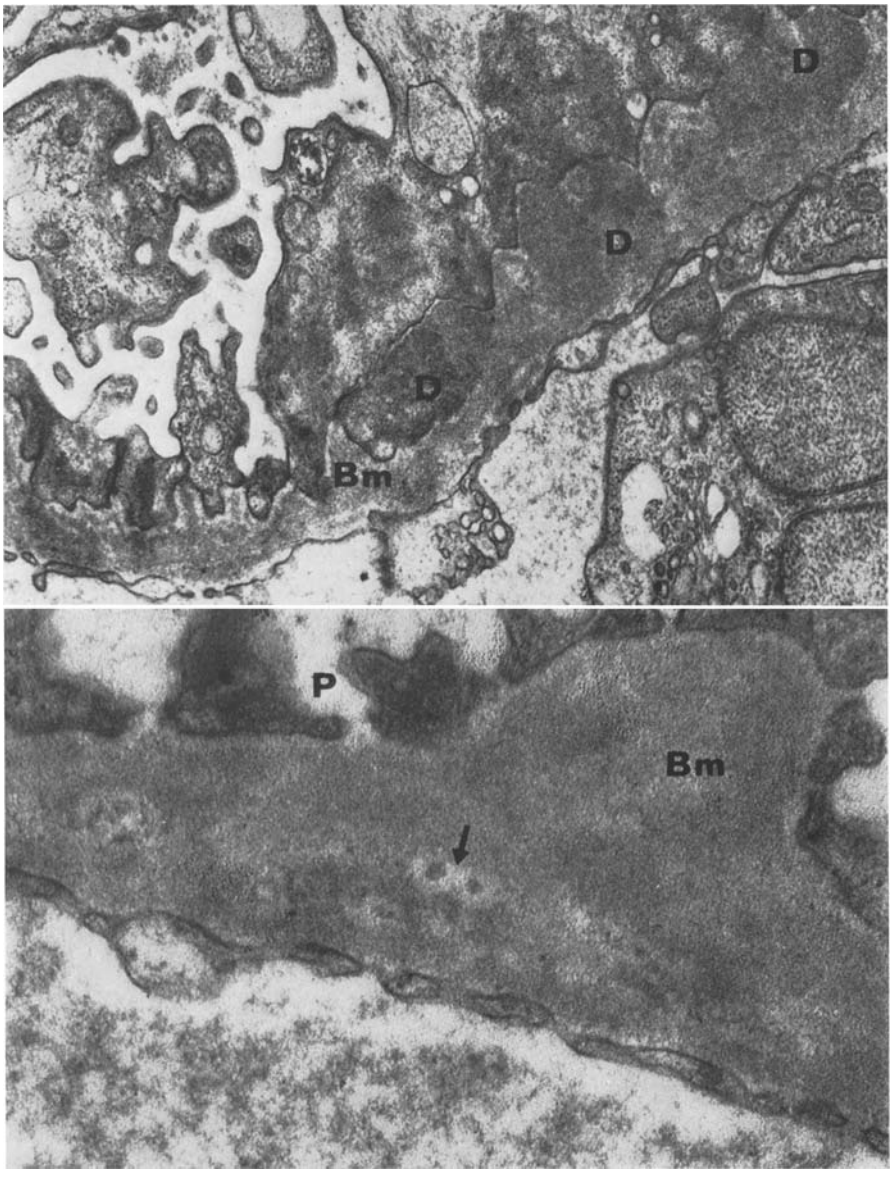

Fig. 5. Case 13. Top: "nephrotic" picture of the first biopsy with massive although not diffuse dissemination of deposits (*D*). Fusion of foot processes. Basement membrane (*Bm*) focally thickened or normal. Classified as early stage of the chronic extramembranous glomerulonephritis. ×24100. Bottom: second biopsy $1^1/_2$ yr later, 12 mth after clinical recovery. Focal protrusions, small dense globules and translucent fissures (*arrow*) within the basement membrane (*Bm*). Restitution of lamina rara externa and foot processes (*P*), even so in the areas of membranous thickening. ×49200

ary changes. Small granulo-flocculent subendothelial deposits were apparent in most biopsies irrespectively of the extrinsic lesions. The findings of multiplied cytoplasmic and membranoid stripes of the *mesangium* corresponded to those of optical microscopy.

Clinico-morphological correlations will be fully discussed in another study: only a selection of important data is presented here.—As appears from the Table 1, the advanced "membranous" glomerulonephritis (No. 1–6) was characterized chiefly by an insidious onset, long duration and heavy proteinuria with nephrotic syndrome; biopsy was performed in the late stage of the disease. In the patients No. 7–11 with discrete "membranous" thickening, biopsy was practised earlier, but here too the gradual "oedematous" onset and nephrotic syndrome prevailed and only in the case No. 11 (proteinuria exceeding 25 g/24 hr, early nephrotic syndrome after acute glomerulonephritis) a marked remission took place. In the case No. 12 and 13 (no "membranous" thickening, slight to moderate endocapillary hypercellularity, multiple but non-diffuse EMD, cf. Fig. 5, top), signs of early or imminent nephrotic syndrome appeared after acute glomerulonephritis. In the former case (No. 12), a remission took place 2 years later while in the latter one (No. 13), the lesion healed 6 months after the first biopsy and the second puncture performed 18 months later revealed only minimal rests of EMD (Fig. 5, bottom). In the case No. 14 (acute glomerulonephritis without nephrotic syndrome), minimal local extramembranous protrusions, similar to those of Fig. 5 (bottom) were recorded 3 months after the onset, in the healed stage.—Thus, the favourable part of our series (No. 6, 11–14) was mostly characterized by an acute onset with or without nephrotic syndrome, discrete to absent "membranous" lesions, an inconstant moderate endocapillary proliferation and florid granular EMD with slight secondary degeneration of the lamina densa. In all these patients an early and adequate steroid (twice also immunosuppressive) treatment was instituted, but such was the case also in most "unfavourable" patients of the upper part of Table 1. Up to the close of this paper, no renal insufficiency was recorded, neither had any of the patients signs of a systemic disease.

Discussion

A common morphological feature of our sample are granular focal deposits or rests thereof, disseminated over the external surface of the glomerular capillary basement membranes. Originally, these EMD were supposed to be focal thickenings of the basement membrane proper (Spargo and Arnold, 1960). They were soon identified, however, as precipitates of diffusible protein substance (Movat, 1959; Movat *et al.*, 1962; Huhn *et al.*, 1962; Galle *et al.*, 1962). A regular positivity of the "bead-like" binding of immunoglobulins and complement, as observed in both clinical biopsy and experiment, considerably supports the assumed immunoprecipitative character of EMD (Lange *et al.*, 1966; Hadley and Rosenau, 1967; Moppert and Fresen, 1967; Heymann *et al.*, 1970). Renal lesions characterized by EMD manifest themselves by considerably variable functional disturbances and course, with markedly preponderant proteinuria and nephrotic syndrome. The general importance of EMD will be discussed from the viewpoint of their pathogenesis, development, sequelae, and possible reversibility.

Pathogenesis of EMD. According to Dixon (1968), two types of basic lesions exist in glomerulonephritis: those caused by local binding of nephrotoxic (mainly anti-basement-membrane) antibodies, and those originating from deposition of circulating immune complexes—involving both the subendothelial and subepithelial spaces. This latter alternative apparently characterizes our sample, in which lesions of capillary periphery strongly prevail (Heptinstall, 1966). The marked resemblance between EMD in man and those of the chronic form of experimental serum sickness is accepted for a serious evidence that both these states are pathogenetically related to each other (Cluskey and Vassalli, 1971; Cluskey, 1971).—In the light of fundamental studies by Dixon *et al.* (1961), the degree and quality of glomerular lesion depend on the antigen/antibody ratio, which governs the molecular size, diffusibility, and further properties of the immune complexes produced. If the antibody response is absent or heavily blocked, then the antigen—possibly non-toxic *per se*—freely diffuses across the intact capillary wall. On the other hand, if antibodies are present in excess, *insoluble* complexes are deposited and/or phagocytosed in the area of endocapillary cells, and in polynuclears as well. Critical for the formation of EMD is the intermediate state between these two extremes, when *soluble* complexes with a moderate excess of antigen are not adequately phagocytosed inside the capillary, diffuse across the basement membrane, and are retained only at the "slit membrane" level. During a protracted (or repeated?) production of such complexes the number of EMD increases, and their dissemination augments as well, up to assume a diffuse character. An important role is doubtlessly also played by the amount of antigen available and the duration of its action (Moppert and Fresen, 1967). The diffusion and deposition of complexes is substantially dependent on the ultrafiltering properties of the capillary wall: in view of the recent experiments done by Karnovsky *et al.* (1969), the very interpedicellar "slit membrane" represents the closest-meshed screen in the glomerular ultrafilter barrier, apparently retaining even proteins with molecular weight lower than 200000, still passing readily through the fenestrated membrane and lamina densa. The soluble phase of immune complexes is indiscernible by electron microscopy, but its diffusion might become manifest by swelling and rarefaction of the lamina densa (Movat, 1959; Movat *et al.*, 1962). In animal experiment, permeation of conjugated ferritin also can be observed (Andres *et al.*, 1963).

In acute glomerulonephritis, EMD are disseminated usually far apart and their number tends to be lower (Hinglais and de Montéra, 1962), indicating that the production period of soluble immune complexes may be short and transient (Germuth *et al.*, 1967). As the antibody response rapidly increases, the subsequently formed poorly diffusible complexes are probably destroyed by endocapillary cells and the preformed EMD are degraded within several weeks to months (Strunk *et al.*, 1964; Herdson *et al.*, 1966; our own case No. 14), leaving minute to minimal local defects. Proliferation of irritated endocapillary cells, however, may lead to chronic mesangial-proliferative or lobular glomerulonephritis. On the other hand, the absence of endocapillary proliferation and presence of multiple EMD in "membranous" glomerulonephritis, would correspond also in the human to protracted (or relapsing) circulation and diffusion of soluble immune complexes (Cochrane, 1971). Irregularity of and fluctuation

in the complex synthesis may explain the combined and intermediate forms with focal endocapillary proliferation and leukocytosis associated with EMD and the focal absence of the latter, as observed in our sample and also described by others (Habib *et al.*, 1961; Germuth *et al.*, 1967). Equally possible is a dense "nephrotic" dissemination of EMD already in the postacute phase (Berger *et al.*, 1963; Herdson *et al.*, 1966; our cases No. 10–13). Both spontaneous and arteficial changes in the character of immune complexes, however, are subject to certain limitations, and clinical biopsy does not reveal a conversion of a typical "membranous" lesion to a proliferative one, neither do EMD appear in lobular glomerulonephritis (Heptinstall, 1966; Pollak *et al.*, 1968; Mandalenakis *et al.*, 1969; also our own experiences).

Involution and Consequences of EMD. The changes in the basement membrane adjacent to EMD apparently are early ones: such changes—discrete at least—were present in all our biopsies. Granular florid EMD show signs of local expansion towards both lamina densa and adjacent podocyte. This augmentation of deposits may be caused by apposition of complement, whose local activation increases the aggressivity of the complex (Glynn and Holborow, 1971). The periphery of EMD is bordered by a narrow translucent rim as early as in the first weeks (Michael *et al.*, 1967); laterally, slender projections of basement membrane material are formed to surround and overbridge the EMD. These Ag-impregnable "spikes" (Jones, 1957; Churg and Grishman, 1959; Movat, 1961) are the first indirect microscopic indicators of the presence of EMD, whose substance itself accepts substantially less silver. In paraffin sections (PAS) at this stage the basement membranes still have a normal appearance, and in routine biopsy a false diagnosis of "minimal" lesion can be stated. On the other hand, in semithin sections stained with toluidine blue, even optical microscopy may reveal slightly uneven external contours of capillary walls.—The EMD having been once buried by membranoid matter, the lamina rara externa and the foot processes, obliterated up to this stage, are restored, partially at least. The regular pattern of EMD substructure is then disturbed, and their sharp contours are blurred: there appears a subepithelial layer of EMD débris with intermingled stripes of membranoid matter. The global thickness grows two- to fivefold and probably continues to increase. In such an advanced "*membranous transformation*" (Churg *et al.*, 1965) it is very hard to recognize the characteristic original EMD. An important sign is the serrated and "bumpy" external contour of the capillary wall, even at the virtual absence of granular EMD. But for the right interpretation of this feature, the overall picture might be classified as a "nonspecific thickening" or a late stage of lipoid nephrosis (Kimmelstiel *et al.*, 1962). A diagnosis of "membranous" glomerulonephritis then becomes easy even in routine biopsy using trivial stains (Allen, 1962). A classical "membranous" picture, as follows, only reproduces advanced secondary involution of the process whose characteristic and most important manifestations, hardly or not at all resolved by optical microscopy, already had passed their course.

Clinico-Morphological Features and Potential Reversibility of EMD. The early and efficient elimination of antigen—an ideal therapeutic and preventive intervention in immune complex disease—may be possible with bacterial antigens.

The participation of the latter in the EMD, especially in their chronic "nephrotic" variants, is dubious in man, and attempts at identification *in situ* of streptococcal antigens have repeatedly failed both in clinical and in experimental conditions (Dixon *et al.*, 1961; Cluskey *et al.*, 1966). Likewise, the viral, or even nuclear autologous origin of antigen in the human "membranous" variant is possible but still not confirmed (Manaligod *et al.*, 1967; Cluskey and Vassalli, 1971).

The primary antigen being unknown and the temporary glomerular ischaemization clinically unfeasible (Germuth *et al.*, 1967b), there remains the possibilities of intervention in the structure and diffusibility of immune complexes. A long-standing arteficial stimulation of antibody response would involve many hazards in the clinic and eventual destructive hypersensitivity lesions would certainly outweigh the profit from a possible disappearance of EMD. Thus, inhibition of antibody response (steroids, azathioprin *et sim.*) remains, for the time being, the best passable way of therapy. A beneficial effect of immunosuppression was proved in early stage of NZB/W disease of mice (Lambert, 1969) and should the pathogenesis of EMD in man be related, then such an intervention could be efficient in the clinic too. Sporadic recent reports are available about actual disappearance of EMD with clinical remission (even for several years) leaving discrete ultrastructural sequelae and exhibiting marked inhibition of local anti-immunoglobulin fixation (Michael *et al.*, 1966, 1967; Pollak *et al.*, 1968; Bariéty *et al.*, 1969; Forland and Spargo, 1969). Such a favourable event apparently occured in our cases No. 11–13, where the disease—as judged by clinical picture and biopsy—was going up to develop into the massive "membranous" glomerulonephritis.

An earliest diagnosis of the EMD without well-developed membranous changes (Churg, 1966) is apparently a *conditio sine qua non* of the prolonged therapeutical success. In fact, long "pre-oedematous" periods of unexamined asymptomatic proteinuria usually precede the bioptical diagnosis of EMD and "initial" nephrotic swellings actually manifest considerable degeneration of basement membranes—the irreversible "membranous" stage of the disease (Hamburger *et al.*, 1966; Forland and Spargo, 1969). Even then, partial remissions can be observed (cf. our case No. 6): perhaps the damaged capillary wall grows less permeable, or inversely, at a highly non-selective proteinuria (Cameron, 1968), lets pass such complexes that would be trapped by the normal capillary barrier.—The question is open, whether the unsatisfactory course in our patients No. 7–10 is due to the actual inefficacy of the suppressive therapy or (rather?) to its too late institution. According to certain studies, a permanent healing should be achieved only in the non-diffuse forms, whereas in diffuse EMD, regardless of the moment of diagnosis and therapy, the outlooks are poor (Ducrot *et al.*, 1969). It may be suspected, however, that *all* forms of EMD, the diffuse "nephrotic" ones included, pass through an *initial non-diffuse stage*(?), capable to heal *ad integrum*, functionally at least.

The differences between typical "membranous" and "proliferative" glomerulonephritis led to speculations about their different origin and to proposals of different terms: membranous glomerulosclerosis, nephrosis or glomerulopathy (Heptinstall, 1966; Cluskey *et al.*, 1966; Pollak *et al.*, 1968; Forland and Spargo,

1969). If, however, Dixon's (1968) and Cochrane's (1971) pathogenetic conclusions are valid in human, then different forms of immune complexes are a basic common factor in both variants, and as long as any essential aetiological difference (e.g. in causative antigen[s]) is not stated, no cogent reason exists to abandon the general comprehensive term "glomerulonephritis". With characteristic primordial lesions of the disease discussed in view, the term *chronic extra-(peri-)membranous glomerulonephritis* seems to be the most adequate one: its correctness would be confirmed and practically justified by an early and effective treatment, and perhaps even prevention of the classical "membranous" lesion, so far representing a frequent (18–36 per cent, Heptinstall, 1966), refractory, and disabling form of nephrotic syndrome.

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Note Added in Proof. After the close of the manuscript, renal biopsy has been repeated in the patient No. 5. Massive and numerous (recurrent?) granular EMD have been found over the thickened glomerular capillary walls.

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