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The Obsolescent Renal Glomerulus – Collapse, Sclerosis, Hyalinosis, Fibrosis

A Light- and Electron Microscopical Study on Human Biopsies*

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Summary. By light and electron microscopical examination it is shown that four structural components can contribute to obsolescent glomeruli: capillary basement membranes, enriched mesangium matrix, "vascular" hyalin and collagen fibers. Each of these components can bring about glomerular damage alone. One non-reactive form – a glomerular collapse with only basement membrane remnants – can be separated from three reactive forms: the accumulation of mesangium matrix (sclerosis or matrix-sclerosis), deposition of vascular hyalin (hyalinosis in the narrow sense), and fiber development within the former urinary space (fibrosis or fibro-sclerosis). The use of the term "fibrinoid" in place of the descriptive term "hyalin" is not supported by objective results. Knowledge of the various constituents which accumulate in the reactive types of glomerular obsolescence might be important in the diagnosis of the underlying disease, though mixed pictures were often observed. To avoid terminological overlap we suggest that the term "hyalinization" is replaced by "obsolescence" or "scarring" with specification of the structural components involved.

Key words: Glomerular obsolescence – Glomerular sclerosis – Glomerular hyalinosis – Glomerular fibrosis.

Introduction

In a wide range of chronic renal diseases glomerular involvement results in glomerular scarring. There are some papers dealing with this subject (Moritz and Hyman, 1934; McManus and Lupton, 1960; Nagle et al., 1969) with diverging opinions and terminological difficulties. We, therefore, decided to re-examine the problem, especially because we felt that the identification of the phenomena

* Dedicated to Prof. Dr. H.W. Altmann on occasion of his 60th birthday

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occuring during the process of obsolescence might be of some importance for diagnostic purposes in glomerulonephritides. In conventionally H.E. stained paraffin sections the glomerular scar, i.e. the obsolescent glomerulus, presents as a more or less homogenous solid eosinophilic nodule, largely devoid of the definite structures. Therefore pathologists have hitherto widely used the term "hyalinization" when describing the general aspect of an obsolescent glomerulus.

In this apparently uniform glomerular end stage lesion four different conditions could be identified by light- and elelctron microscopical examination. In the following report a detailed pathomorphological analysis of the structural components involved is presented.

Material and Methods

A collection of about 3500 renal biopsy specimens obtained from adults and infants, representing a wide spectrum of renal diseases was available for this study, and included the various known types of glomerulonephritides, glomerulopathies of different etiologies – among these diabetic glomerulosclerosis –, vascular alterations and interstitial processes. Obsolescent glomeruli with its variants described in this paper were found practically in all nephropathies, resulting as well from primary (inflammatory and non-inflammatory) glomerulopathies as secondarily to primary extraglomerular (e.g., vascular, interstitial) lesions. This is particularly true for progressed stages of nephropathies in which various conditions above mentioned are combined. Therefore an exact listing of the diagnoses concerning types and numbers of cases is renounced. The special problems of glomerular involution in early infancy were excluded from this study.

Tissue pieces assigned for light microscopical examination were fixed in 4% buffered formalin solution. 3 to 4 µm thick routine paraffin sections (40–50 serial sections per case) were stained with H.E., Goldner's trichrome, Pearse and PAS stain. Additionally silver impregnation was carried out on selected cases (Jones-Chromotrop R according to Ehrenreich and Espinosa, 1971).

For electron microscopy small tissue blocks were cut from either end of the biopsy specimen immediately after operation and either fixed in cold 3% phosphate buffered glutaraldehyde solution (pH 7.3) and postfixed in 1% osmium tetroxide for 1 to 2 h, or fixed immediately in osmium tetroxide solution, dehydrated, and embedded in Epon 812 1 µm thick sections were stained with methyleneblue or silver methenamine, thin sections with uranyl acetate and lead citrate. Examination was done in a Siemens Elmiskop I or a Philips 300 elelctron miscroscope.

Results

Rewiew of the light microscopic material revealed that in individual cases one special type of obsolescent glomeruli sometimes dominate the histological picture, but mixed populations of differently appearing obsolescent glomeruli were frequently observed in individual cases. The question of whether predominance of a special type of obsolescent glomerulus may be indicative of the pathogenetic way by which glomerular damage has been produced is still under investigation and not the objective of this study. Here, only the general structural aspects of obsolescent glomeruli will be described.

At first, some preliminary remarks on the terminology used may be helpful: The four tissue components which may appear combined or with one feature predominant in obsolescent glomeruli, are designated as sclerosis (matrix-sclerosis), hyalinosis, fibrosis (fibrosclerosis) and collapse. It

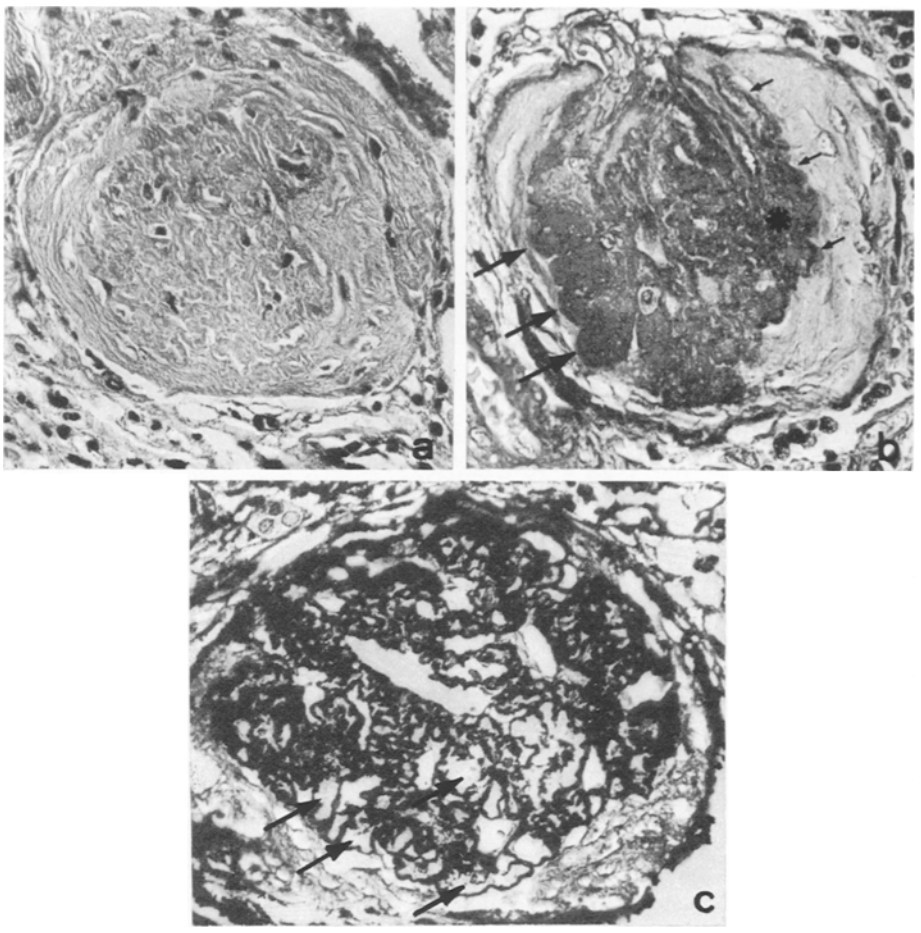


Fig. 1a–c. Histological appearance of obsolescent glomeruli. **a** H.E. stained specimen. **b** The Pearse stained specimen demonstrates four components: capillary basement membranes (*small arrows*), mesangium matrix (+), hyalin nodules (*big arrows*), and a fibrous scar, which encircles the central tuft portion. **c** After Jones-Chromotrop R staining the basement membrane component becomes especially prominent. The arrows point to some of the hyalin filled areas (original: red). The fibrous component exhibits a poor argyrophilia. a–c: × 340

will be shown that the last represents the acellular remnants of a glomerulus in particular the basement membranes. Sclerosis and hyalinosis reveal an increase in mesangium matrix or an accumulation of "vascular" hyalin respectively, whereas glomerular fibrosis is characterized by the development of collagen fibers within the urinary space.

Light Microscopy

The simplest form of glomerular obsolescence was collapse with only the former capillary and capsular basement membranes and some mesangium matrix re-

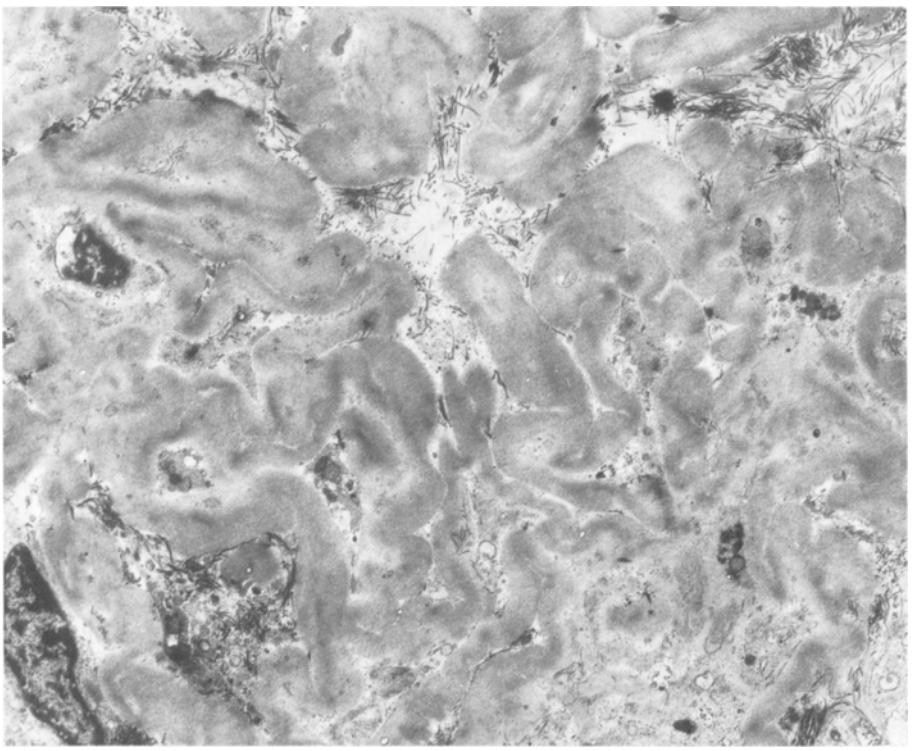


Fig. 2. Basement membranes as main substrate of glomerular collaps. Portion of a collapsed glomerulus demonstrating relatively well preserved basement membranes. Electron micrograph. ×3850

maining (Fig. 6a). Collapsed glomeruli were especially small (about 65 μm) because of dense packing of the highly wrinkled basement membrane remnants.

Most glomeruli had become obsolescent from the accumulation of several structural components often appearing simultaneously: Figure 1a shows the typical aspect of such a glomerulus when stained with hematoxylin-eosin: a solid nodule with some occasional cells, but no further detail visible inside. The diameter (about 120 μm) rarely exceeded two thirds of that of the funcional and expanded glomerulus (about 200 μm). After application of more differential stains (Fig. 1 b and c) structural details appeared which permitted us to separate a tuft element from a surrounding sickleshaped "extracapillary" component, obviously occupying the former urinary space.

The tuft element contained up to three structural components:

A distinct feature were the PAS- and silver positive ghosts of the capillary *basement membranes* which formed the peripheral rim of the tuft (Fig. 1 b and c). The former endocapillary space, i.e. the area enclosed by the basement membrane remnants of the tuft, was occupied by a variable amount of one or two amorphous substances. One of these presented the distinct staining properties of the *mesangium matrix*: it gave a PAS- and silver positive reaction

while presenting a slightly irregularly dense, partly coarsely granular, partly wavy appearance (Fig. 1b, Fig. 6b). A further substance presented a distinct hyalin appearance in the light microscope (Fig. 1b, Fig. 6c) similar to or identical with the *hyalin* of arteriolar walls in, for instance, hypertensive or diabetic lesions. In contrast to the mesangium matrix this substance stained weakly with PAS, strongly with orange G and proved to be silver negative (Fig. 1b and c; Fig. 6c). As a rule the hyalin component formed small nodules in the site of the former capillary lumina, or irregular patches within the increased mesangium matrix.

Surrounding the tuft portion, a further component had developed within the former urinary space (Fig. 1b and c; Fig. 6d): This hardly stained with PAS (Fig. 1b); the silver impregnation gave variable weak positive results (Fig. 1c); the trichrome stain, however, was highly suggestive of the presence of *fibers*.

Bowman's capsule often was also altered. It frequently appeared thickened or split and sometimes large segments were completely absent. Now and then nodules of hyalin of varying size were deposited within the capsule. Some rare cases exhibited a periglomerular fibrosis.

Electron Microscopy

Electron microscopical examination confirmed the presence of various structural elements within obsolescent glomeruli:

a) Basement Membranes. All obsolescent glomeruli examined contained comparatively well preserved basement membranes (Fig. 2; Fig. 3a). These were lacking the covering endothelial and epithelial cells over large areas. Collapsed glomeruli (Fig. 2) consisted predominantly of basement membranes and small amounts of mesangium matrix, some cellular debris and single small fibers.

b) Mesangium Matrix. The PAS-positive and argyrophilic endocapillary component demonstrated ultrastructurally a finely fibrillar structure, largely indentical with the mesangium matrix (Fig. 3). Enclosed were a few cells of endocapillary origin. They appeared atrophic, while demonstrating a small cytoplasmic rim around the central nucleus, with few swollen mitochondria, widened cisternae of rough endoplasmic reticulum, some myelin figures and lysosomal residual bodies. Furthermore, there were intermingled areas consisting of cellular debris and small foci in which fibers had developed. The diameters of these fibers ranged from less than 50 Å to up to 300 Å, the thicker ones exhibiting a weak cross striation (Fig. 3b). Very rarely a thicker collagen fiber with a 660 Å periodicity of cross striation was seen.

c) Hyalin. The light microscopically hyaline material which was orange G positive showed a homogenous appearance when examined in the electron microscope (Fig. 4a). High power elelctron micrographs revealed a distinct granular pattern (Fig. 4b), each "granule" about 100 Å in diameter. This substance occured

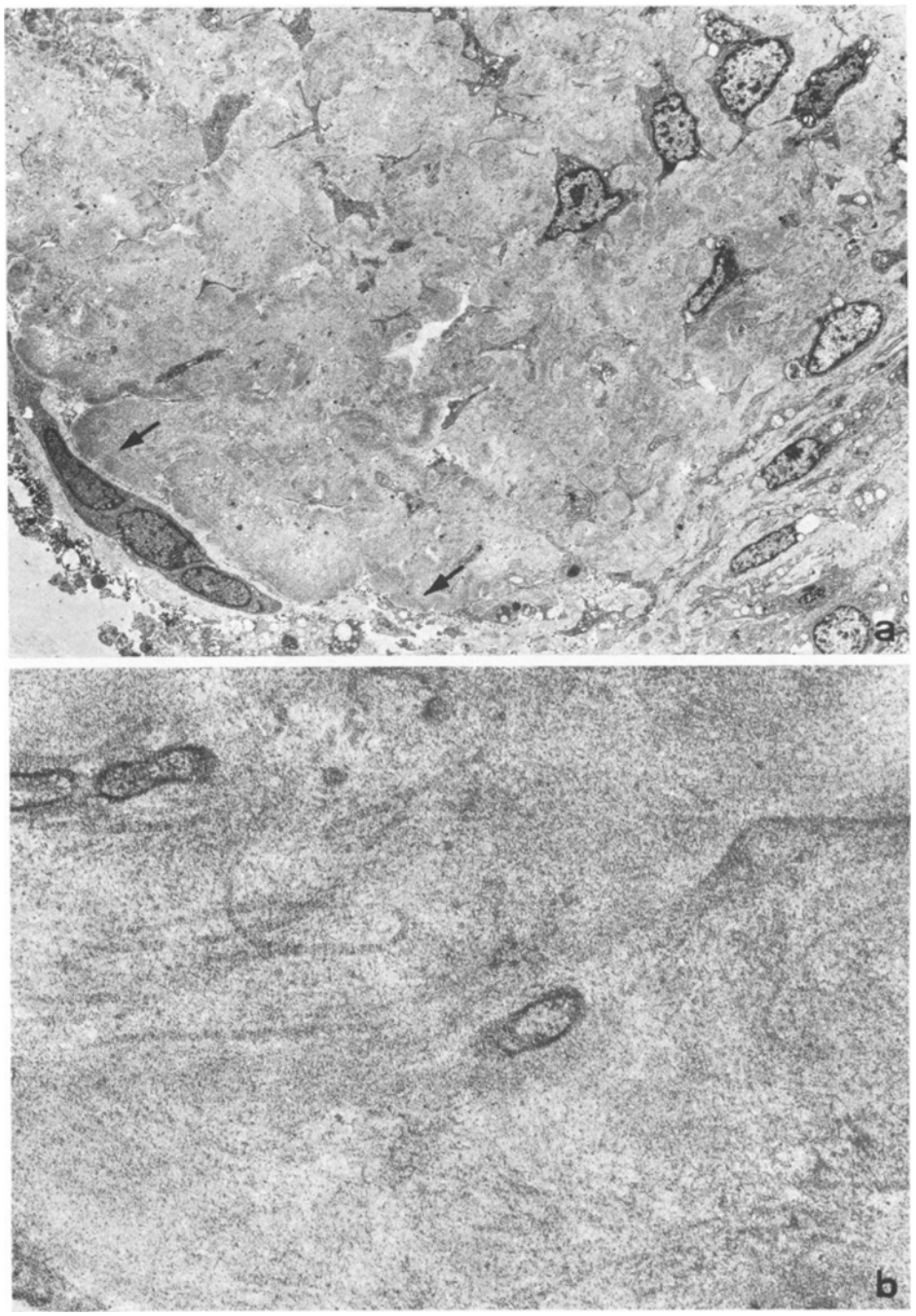


Fig. 3a and b. Mesangium matrix as main substrate of glomerular (matrix) sclerosis. **a** Low power electron micrograph showing an abundance of mesangium matrix, in between which some atrophic cells have survived. The periphery is formed by capillary basement membrane ghosts (→). ×325(**b** Finely fibrillar mesangium matrix as seen in higher magnification. Some small fibers are present. ×59,200

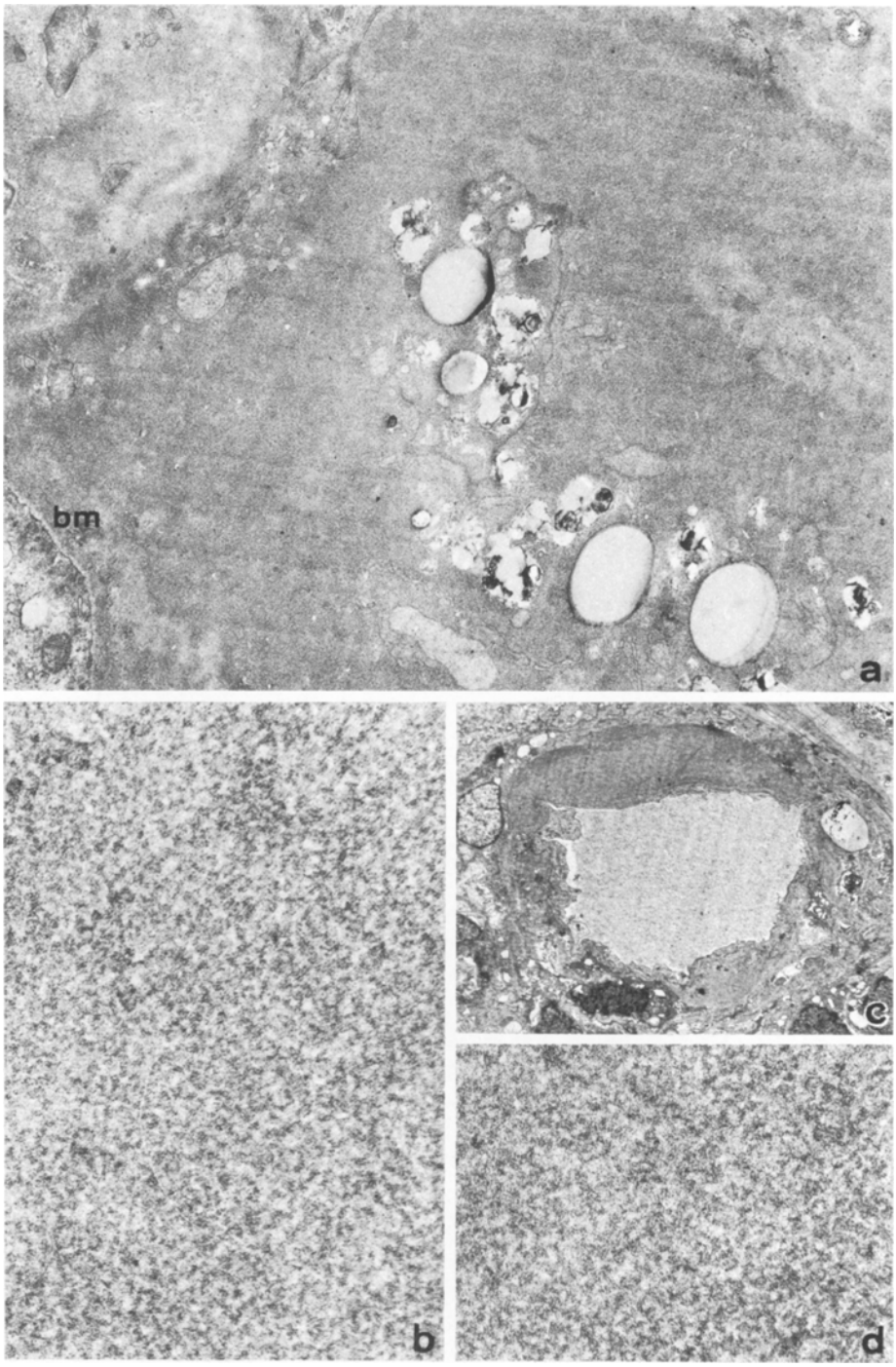
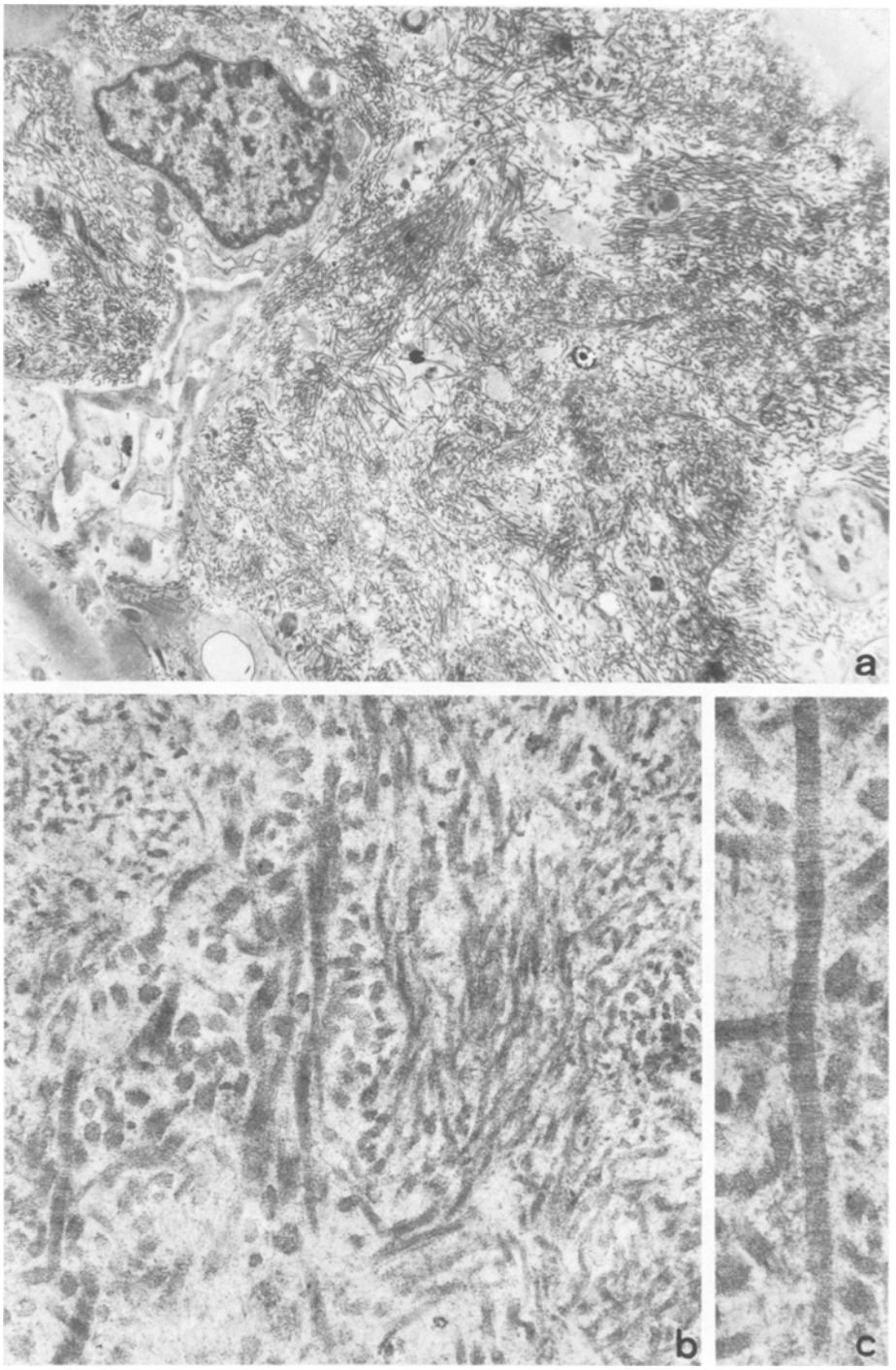


Fig. 4a–d. Hyalin as main substrate of glomerular hyalinosis (in a narrow sense). **a** and **b** Glomerular hyalin. **c** and **d** Vascular hyalin. **a** Hyalin nodule, which occupies a capillary loop. BM = basement membrane. × 13,000. **b** The high power view gives a distinct granular appearance. × 99,000. **c** Segmental hyalin deposition within the wall of a renal arteriole. × 1680. **d** High power micrograph of hyalin in picture c, demonstrating the ultrastructural similarity of vascular and glomerular hyalin. × 99,000



Figs. 5a–c. Fibers as main substrate of glomerular (fibro-)sclerosis. **a** Irregular oriented fibers occupying the urinary space. Bowman's capsule in the lower left corner, capillary basement membrane segment in the upper right corner. ×6840. **b** Collagen fibers showing a widely varying thickness, many of them are ill defined. ×52,500. **c** Collagen fiber with typical periodic cross striation. ×75,800

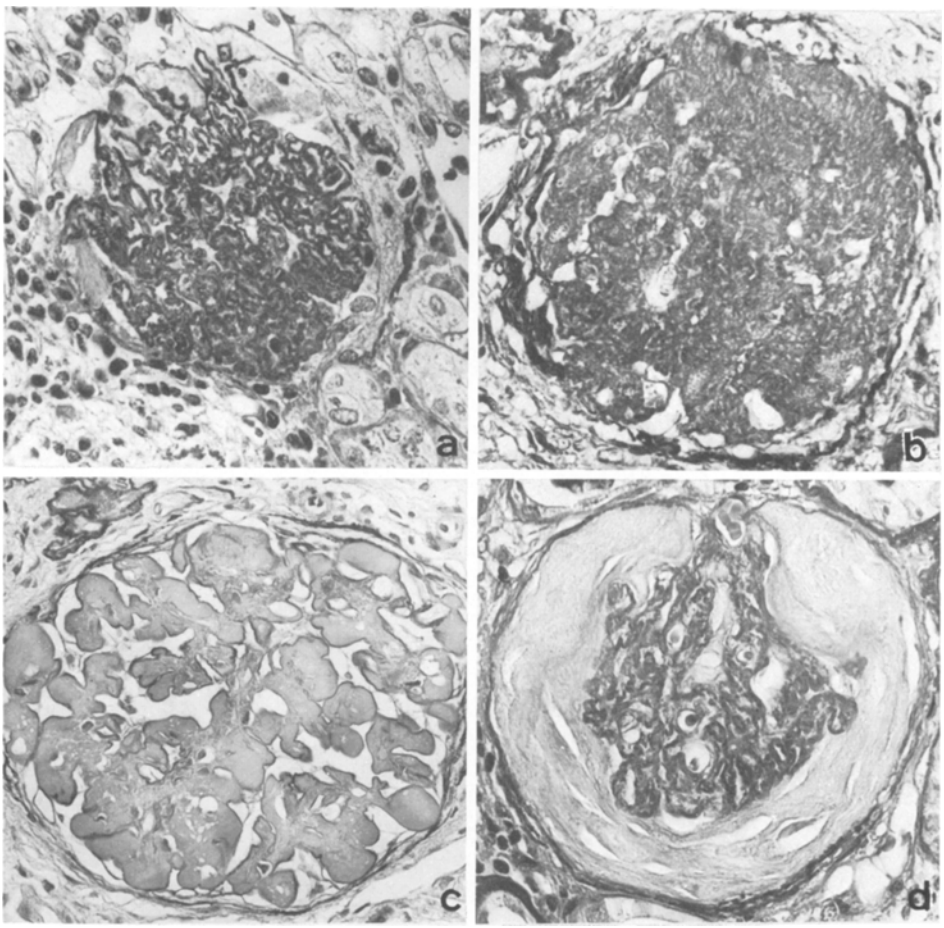


Fig. 6a–d. "Pure" forms of glomerular obsolescence: **a** Collapse, **b** sclerosis, **c** hyalinosis and **d** fibrosis. a–d: PAS ×530

at the site of the former capillary lumina or within the mesangium matrix, in a nodular or less defined patchy arrangement.

Sometimes clear roundish droplets – presumably lipid in nature – were enclosed. Fibrillar material, especially fibrin, was never seen in the hyalin material. In a few cases of focal and segmental sclerosing glomerulopathy fibrin strands were situated focally in subendothelial locations within the capillary wall; the hyalin nodules themselves, however, did not contain fibrin fibrils.

The hyalin change of renal arteriolar walls was also examined, and exhibited identical ultrastructural features (Fig. 4c and d).

d) Collagen Fibers. Electron microscopical examination of the former urinary space revealed that the obliteration was due to numerous randomly oriented fibers (Fig. 5a–c). These showed varying diameters (120 to 600 Å). Thick exam-

ples exhibited a periodic cross striation characteristic for collagen fibers (Fig. 5b and c). In between the fibers few cells were seen, which were small in size and characterized by an oval nucleus and a small rim of cytoplasm, poor in organelles, among these were a few mitochondria and RER cisternae. The plasma membrane was partly accompanied by a thin basement membrane.

The capsule of obsolescent glomeruli also showed severe alterations. The epithelial cells had perished, only a few had survived. The basement membrane was best preserved, but mostly thickened and split; in cases wide segments were absent. Occasionally hyalin nodules were enclosed, which exhibited the finely granular appearance of the tuft and vascular hyalin, as described above.

Thus it appears that increase in mesangium matrix (sclerosis), deposition of "vascular" hyalin (hyalinosis), and fiber formation (fibrosis) are the main conditions which contribute to glomerular obsolescence. Though all these components are often present together each component may, by itself, produce obliteration as well. Figure 6 gives representative examples of such largely pure variants: obsolescence caused by sclerosis (Fig. 6b), hyalinosis (Fig. 6c), fibrosis (Fig. 6d) and in contrast to the former types, glomerular collapse (Fig. 6a).

Discussion

The subject of our investigations was a glomerular condition which is widely described as glomerular "hyalinization" (Allen, 1962; Anderson and Jones, 1971; Robbins, 1974; Zollinger, 1974). For this reason it seems reasonable to open this discussion with some remarks on the term "hyalin".

Hyalin is a descriptive term, which is frequently applied to any acidophilic, homogenous, refractile, glossy appearing cell or tissue component. Recent German textbooks of pathology distinguish three basic forms of hyalin: epithelial or intracellular, connective tissue, and vascular hyalin (Eder and Gedigk, 1974; Sandritter and Beneke, 1974).

The use of the term hyalin often implies the avoidance of a more detailed characterization. Indeed, when the nature of a hyalin appearing tissue component is not known, this term (hyalin, applied adjectivally) is helpful. But in all those cases in which it can be defined more exactly this should be done, for the sake of accuracy and clarity. This is particularly true for the obsolescent glomerulus, because description of glomerular obsolescence as glomerular hyalinization has concealed the fact that a morphological separation into subtypes is possible. These types have been described above as glomerular collapse, sclerosis, hyalinosis (in a narrow sense), and fibrosis.

As a general principle two methods of glomerular obliteration can be distinguished: first, a *non-reactive* type, represented by glomerular collapse, and secondly and more important, those modes of obliteration which are produced by a *reactive* material accumulation. Table 1 gives a survey of the light and electron microscopical characteristics.

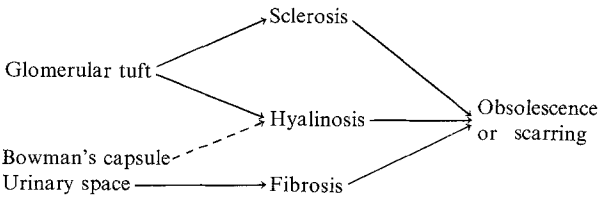
The table again includes the term hyalinosis, but this time it stands for a morphologically relatively well characterized substance with specified staining and ultrastructural attributes, which

Table 1

Type of obsolescence		Light microscopy			Electron microscopy
		PAS	Silver	Orange G chromotrope R	
Non reactive:	Collapse	++	++	−	Basement membrane ghosts
Reactive:	Sclerosis	++	++	−	Finely fibrillar material with some thin fibers = mesangium matrix
	Hyalinosis	+	−	++	Finely granular material identical with vascular hyalin of arterioles
	Fibrosis	(+)	+	−	Collagen fibers

give the "hyalin" appearance in a very pronounced way. A more detailed discussion on this subject is given below when considering on glomerular hyalinosis.

The development of each of the reactive conditions is tightly bound to the structural elements of the glomerulus:



The scheme suggests that obliterating sclerosis and hyalinosis become established within the glomerular tuft, but fibrosis within the urinary space.

Glomerular Sclerosis

Increase in mesangium matrix in inflammatory and non inflammatory glomerular diseases is widely designated as sclerosis (Habib, 1973; Hyman and Burkholder, 1974; Rumpelt and Thoenes, 1974; Churg and Grishman, 1976). Therefore glomerular obsolescence induced by a progressive matrix accumulation should be described as glomerular obsolescence by sclerosis: it might be expected that sclerosing glomerular diseases, as for example focal and segmental sclerosing glomerulopathy (focal glomerulosclerosis) and diabetic nodular glomerulosclerosis, should preferentially (not exclusively, see below in the discussion of hyalinosis) undergo obliteration by sclerosis.

The mesangium matrix is believed to be produced by the cells of the mesangium (de Martino et al., 1976). The matrix exhibits a finely fibrillar structure and encloses small foci of collagen fibrils in pathological conditions in man (Rumpelt and Thoenes, 1974; Churg and Grishman, 1976). In rats collagen

fibrils were found even in normal animals (Latta, 1961; personal observations). Thus, it was not an unexpected finding that collagen fibers also occur in sclerosed glomeruli; in all the cases examined groups of irregularly oriented fibers of varying diameters and varying distinctness of cross striation were enclosed. The matrix, however, always exceeded the fibrous component quantitatively. Cellular debris, presumably remnants of endothelial and mesangium cells, might also occupy larger areas.

The biochemical nature of the mesangium matrix is not well known, but despite its structural resemblance to basement membrane, basic differences must exist. Thus, for instance, collagen fibers develop exclusively within the matrix but never in the basement membranes. Furthermore, both components show a different sensitivity to the venom of certain snakes in both man and experimental animals. The venom damages the matrix but has little or no effect on the basement membranes (Churg and Grishman, 1976).

Glomerular Hyalinosis

Glomerular obsolescence by hyalin accumulation in its pure form is rare. More often hyalin accompanies some other change, especially in focal glomerular sclerosis. Other authors have designated this substance as fibrinoid (Habib and Gubler, 1971; Heptinstall and Joekes, 1971). However, Wagner (1967) has statet that "it is exceedingly difficult to limit the definitions (of hyalin and fibrinoid) by useful quantitative criteria". In our experience fibrin is not demonstrable in the hyalin nodules by means of electron microscopy and is only rarely found in other portions of the capillary wall (Rumpelt and Thoenes, 1974). Additionally, the immunoflorescence technique has not provided proof of a regular occurence of fibrin within the hyalin material. In focal and segmental sclerosing glomerulopathy, in which hyalin is frequently found in large quantities, the examinators could identify fibrin/-ogen, but only in a few cases and then in only minimal quantities (Human and Burkholder, 1973, 1974; Rumpelt and Thoenes, 1974; G.H. Thoenes, 1974). Moreover, the pattern of distribution did not match the typical nodular hyalin deposition. Jenis et al. (1974) failed to find fibrin/ogen, though their electron microscopic material included cases with typical nodular hyalin. Finally it seems possible that the immunohistological fibrin/ogen labelling technique may be not as highly specific as believed, so that positive results may perhaps not always be evidence of the presence of fibrin/ogen (G.H. Thoenes, personal communication). For these reasons we prefer the term hyalin, firstly to avoid possible confusion of hyalin with fibrin or with fibrinoid as it is seen, for instance, in eclampsia, and secondly, since its light- and electron microscopical appearance suggests that it is identical with the "vascular hyalin" in the arteriolar hyalin lesion. Thus we regard hyalin deposited in the glomerulus to be a vascular hyalin of special localisation.

The nature of vascular hyalin and its evolution remains obscure (for review see Wagner, 1967). There are two major theories of the pathogenesis of hyalin arteriolopathy. One hypothesis regards hyalin as a degenerative process in vessel wall constitutents such as smooth muscles (Montgomery and Muirhead, 1954;

Muirhead et al., 1957) or basement membranes (McGee and Ashworth, 1963; Wiener et al., 1965; Carstens and Allen, 1970; Amano, 1977). An opposing view considers hyalin to be hematogenous in origin (Biava et al., 1964; Salinas-Madrigal et al., 1970; McKinney, 1962). These authors suggest an incorporation of plasma proteins, including fibrin, into the vessel wall.

However, in our material supporting evidence was found for neither of the hypothesis. Glomerular and arteriolar hyalin could be easily separated from basement membranes because of its distinct granular appearance, and smooth muscle cells are not a constituent of glomerular capillary walls. Moreover it is of interest, in this connection, that hyalin can also be found in Bowman's capsule which has no direct contact with vessels and blood constituents. This may indicate that synthetic activities of the local cells (other than those related to basement membrane) may be involved in hyalin formation.

Glomerular hyalin deposition is observed in many glomerulopathies, in particular in diabetics and in focal-segmental sclerosing glomerulopathy (Habib et al., 1971; Habib, 1973; Hyman and Burkholder, 1973; Rumpelt and Thoenes, 1974). This is why Habib has called this lesion "Hyalinose segmentaire et focale" (Habib et Gruber, 1971). In our experience hyalin, as a rule, is a secondary phenomen in this type of glomerulonephritis but is nevertheless of considerable diagnostic value.

Glomerular Fibrosis

Pronounced formation of collagen fibers within the urinary space is observed as a late result of crescent formation in extracapillary glomerulonephritis (Min et al., 1974; Olsen, 1974; Dunnill, 1976) and also in renal vascular lesions and in interstitial nephritides. Urinary space fibers differ in structure from the well organized interstitial renal reticulin fibers in that they are not arranged in bundles but show an irregular distribution. Furthermore they have largely varying diameters and variably distinct cross striation. Perhaps these features are reasons for the poor argyrophilia of these fibers.

With regard to their origin the following cell types may be involved:

a) The parietal epithelium of Bowman's capsule, b) the visceral epithelial cells, which participate in crescent formation as shown by Gabbert and Thoenes (1977), and c) fibrocytes, which might reach the urinary space via defective parts of the capsule at the interface with the periglomerular connective tissue. The origin of the collagen synthesising cells within the fibrous crescents cannot be determined from the end stage pictures examined and will have to be followed more accurately in earlier stages of crescent formation.

Glomerular obsolescence is usually brought about simultaneously by diverse components (mesangium matrix, hyalin, collagen fibers). Nevertheless we are under the impression that there are some associations between the basic disease and the predominance of one or the other component. An awareness of the obliterating components and their appearance during the development of glomerular lesion may therefore have a partial diagnostic value. This is less likely to be true at the stage of complete obsolescence, but is important during the

development of a glomerular lesion which might bring about obsolescence. To avoid terminologic overlapping we suggest that the term "hyalinization" is avoided and is replaced by "obsolescence" or "scarring" with specification of the structural components involved.

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