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Glomerulonephritis

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Cellular and Histopathologic Consequences of Immunologically Induced Experimental Glomerulonephritis

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With 14 Figures

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I. Introduction

It is now generally accepted that many, if not all, human cases of glomerulonephritis develop on the basis of immunologic mechanisms. Several key developments in experimental studies have contributed to our current understanding of the pathogenesis of glomerulonephritis.

The first historical step in the field of experimental glomerulonephritis was taken by MASUGI about 40 years ago. Employing heterologous antikidney sera (nephrotoxic sera), he produced and thoroughly described a variety of glomerular diseases in animals compatible with acute, subacute, and chronic glomerulonephritis in humans (MASUGI, 1933; MASUGI, 1934). This experimental model (Masugi nephritis or nephrotoxic nephritis) is distinct from others because of its high reproducibility. Advances in methodology made it possible to analyze the underlying mechanisms responsible for the induction of Masugi nephritis (KAY, 1940; HAMMER and DIXON, 1963; FUJIMOTO *et al.*, 1964). It has been clarified that Masugi nephritis is basically a biphasic disease consisting of the first phase (initial or heterologous phase) and the second phase (secondary or autologous phase). In the first phase, nephrotoxic antibodies (NTAbs) are immediately localized along the glomerular basement membrance (GBM), with or without the immediate onset of glomerular lesions owing to the nature and amount of the NTAbs administered; the second phase occurs several days later following the formation of specific host antibodies that react with the antigen (NTAbs) fixed in the glomerulus resulting in either exacerbation or initiation of glomerular lesions (reviewed by: UNANUE and DIXON, 1967b; MCCLUSKEY and VASSALLI, 1969).

The next outstanding progress in this field was made through studies on experimental acute serum sickness produced by a single i.v. injection of a large amount of foreign serum (RICH and GREGORY, 1943; RICH, 1947) or purified foreign serum antigen (HAWN and JANEWAY, 1947). Studying this "one-shot" serum sickness, special attention was directed to the host immune response in relation to the induction of serum sickness inflammations. The results obtained indicated that various tissue injuries, including proliferative glomerulonephritis, developed at the time of antigen–antibody interaction in the circulation (GERMUTH, 1953). Further investigation disclosed that the formation of antigen–antibody complexes (usually antigen excess, soluble complexes) and their tissue depositions were the major pathogenesis of acute serum sickness diseases (DIXON *et al.*, 1958). The pathogenetic role of antigen–antibody complexes was again confirmed in experimental chronic serum sickness (DIXON *et al.*, 1961). Probably considerable numbers of experimental or naturally occurring nephritis in animals may develop on the same immunologic basis as revealed in experimental serum sickness. It was also proposed that autoimmune disorders including lupus-like nephritis developed under the condition of prolonged antigenic stimulation, correlating with characteristic immune system alterations (OKABAYASHI, 1964).

Another important item of information comes from the observation that renal glomeruli can be damaged by autologous antikidney antibodies produced by repeated immunization with heterologous or homologous kidney antigens. At present, two well established models are available as examples (HEYMANN *et al.*, 1959; STEBLAY, 1962).

In this review, we will describe pathologic processes in these glomerular diseases with some emphasis on their ultrastructural features.

II. Immunologic Basis of Glomerular Injury

In immunologically induced glomerulonephritis, there can be at least three possible patterns of immunologic processes taking place in renal glomeruli, particularly around the GBM as shown in Fig. 1.

In the first type the GBM *per se* acts as an antigen that is capable of reacting with either heterologous or autologous anti-GBM antibodies in the circulation. A typical example is the first phase of rat Masugi nephritis in which rabbit NTAbs combine with rat GBM in a characteristic continuous, linear fashion as revealed by the fluorescent antibody method (ORTEGA and MELLORS, 1956; ANDRES *et al.*, 1962; SEEGAL *et al.*, 1962). The antigen (rat GBM)–antibody interaction and the concurrent participation of complement (C3) usually result in the immediate onset of glomerulonephritis (UNANUE and DIXON, 1964). A similar mechanism may also be operative in other glomerular diseases produced after injection of heterologous antitissue sera that contain cross-reacting antibodies against the GBM (SEEGAL *et al.*, 1963; CHASE *et al.*, 1972). Another example is sheep nephritis caused by repeated injections of heterologous GBM antigen incorporated in Freund's complete adjuvant (STEBLAY, 1962). By the immunization, autologous anti-GBM antibodies are formed in the sheep and are then deposited in the glomerulus with a resultant induction of severe glomerulonephritis.

The second type is mediated by the interaction between an antigen previously localized on the GBM and a specific host antibody in the circulation, as seen in the second phase of Masugi nephritis. In this situation the NTAbs behave as an antigen. Therefore, a significant difference exists between the first and the second phase with regard to the sequence of immunologic events, although the importance of the NTAbs is critical for both occasions. Since the NTAbs have been localized diffusely along the GBM, the host antibody also distributes in a similar continuous linear fashion in immunofluorescence (ORTEGA and MELLORS, 1956). It is tempting to assume that some other antigens, which have no specific affinities to the glomerular constituents, are first deposited on the GBM and then interact with circulating antibodies. However, in no instances has this possibility been clearly proved.

The third type results from glomerular depositions of antigen–antibody complexes initially formed in the circulation. A well known model of this glomerulonephritis is seen in experimental acute serum sickness induced in rabbits by i.v. administration of a large amount of antigen, e.g. bovine serum albumin (BSA). Glomerular localizations of antigen–antibody complexes and complement (C3), are demonstrated by immunofluorescence (DIXON *et al.*, 1958; FISH *et al.*, 1966). The distribution pattern of the complexes is distinctly different from that seen in Masugi nephritis and is characterized by granular fluorescence scattered discontinuously on the capillary wall. The incidence of acute serum sickness nephritis is less frequent than Masugi nephritis since neither antigen nor antibody possesses any affinities to the glomerular constituents.

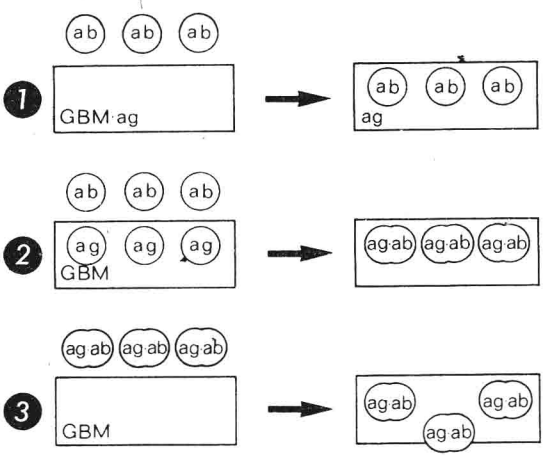
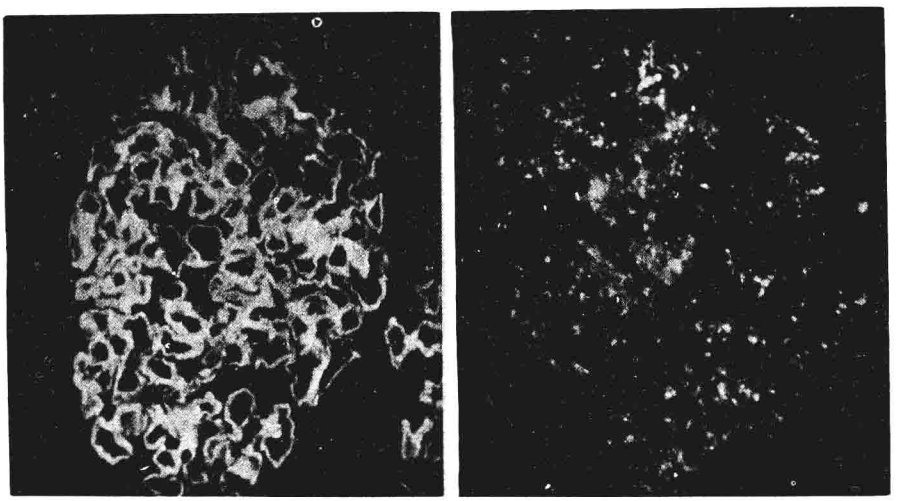


Fig. 1. Three possible immunologic processes occurring around the glomerular basement membrane (GBM). (1) Interaction between endogenous GBM antigens (ag) and circulating heterologous or autologous anti-GBM antibodies. (2) Interaction between antigens previously fixed on the GBM (ag) and circulating antibodies (ab). (3) Deposition of circulating antigen–antibody complexes (ag·ab) which have no specific affinities to the glomerular constituent



a b

Fig. 2. (a) A fluorescent micrograph of a rat glomerulus in the first phase of Masugi nephritis. Characteristic linear localization of nephrotoxic rabbit IgG. ×500. (Courtesy of Dr. H. TOMIOKA.) (b) A fluorescent micrograph of a rabbit glomerulus in acute serum sickness nephritis. Discrete, finely granular fluorescence demonstrating deposition of rabbit IgG along the capillary walls and in the mesangium. ×540. (Courtesy of Dr. M. SANO)

Such a mechanism as shown in serum sickness nephritis would account for the pathogenesis of a number of acute as well as chronic experimental glomerulonephritis cases and various substances, e.g. foreign proteins, infec-

tious agents, or endogenous cell and tissue components might serve as antigenic constituents of the nephritogenic immune complexes.

III. Morphologic Aspects of Immunologically Induced Glomerulonephritis

Although there have been many excellent publications dealing with pathologic features of immunologically induced glomerulonephritis, the references cited here will be limited to those concerned with the ultrastructural pathology and possible pathogenesis.

1. Masugi Nephritis

NTAbs are prepared in an animal by immunization with the kidney from a different species of animal. Masugi nephritis is elicited by a passive administration of the NTAbs into the donor animal of the kidney antigen and is divided into two phases. In general, definite glomerular changes are seen both in the first and the second phase when mammalian NTAbs are employed, whereas fowl NTAbs are not nephritogenic during the first phase. It has been demonstrated that the major nephritogenic antigen is included in the GBM (KRAKOWER and GREENSPON, 1951; CRUICKSHANK and HILL, 1953).

a) The First Phase of Masugi Nephritis

Pathologic processes during the first phase have been extensively analyzed in rat Masugi nephritis produced by injection with rabbit NTAbs (PIEL *et al.*, 1955; MILLER and BOHLE, 1957; CHURG *et al.*, 1960; FELDMAN *et al.*, 1963; FUJIMOTO *et al.*, 1964; COCHRANE *et al.*, 1965). The rabbit NTAbs are fixed to the GBM immediately after injection and persist for at least several months (ORTEGA and MELLORS, 1956; SEEGAL *et al.*, 1962). Localization is visualized by immunofluorescence in a uniform, linear pattern. Fixation of rat or guinea pig complement is also seen in a similar fashion (BURKHOLDER, 1961; VOGT and KOCHEM, 1961; UNANUE and DIXON, 1964). Glomerular changes shortly after injection of the NTAbs are recognizable only by electron microscopy, consisting of a slight loosening of the mesangium and circumscribed subendothelial accumulation of electron lucent material accompanying the detachment of the endothelial lining. More definitive changes are observed after several hours. There is a variable thickening of the GBM and local depositions of wispy, poorly delineated substances within or at the luminal side of the GBM (FELDMAN, 1963). Attenuated portions of the endothelium are often desquamated from the GBM so that the GBM is exposed directly to the capillary lumen. Simultaneously, accumulations of polymorphonuclear leukocytes (PMNs) are seen in the capillary tufts. An intraluminal aggregation of platelets and fibrin can also be seen in varying degrees depending upon the

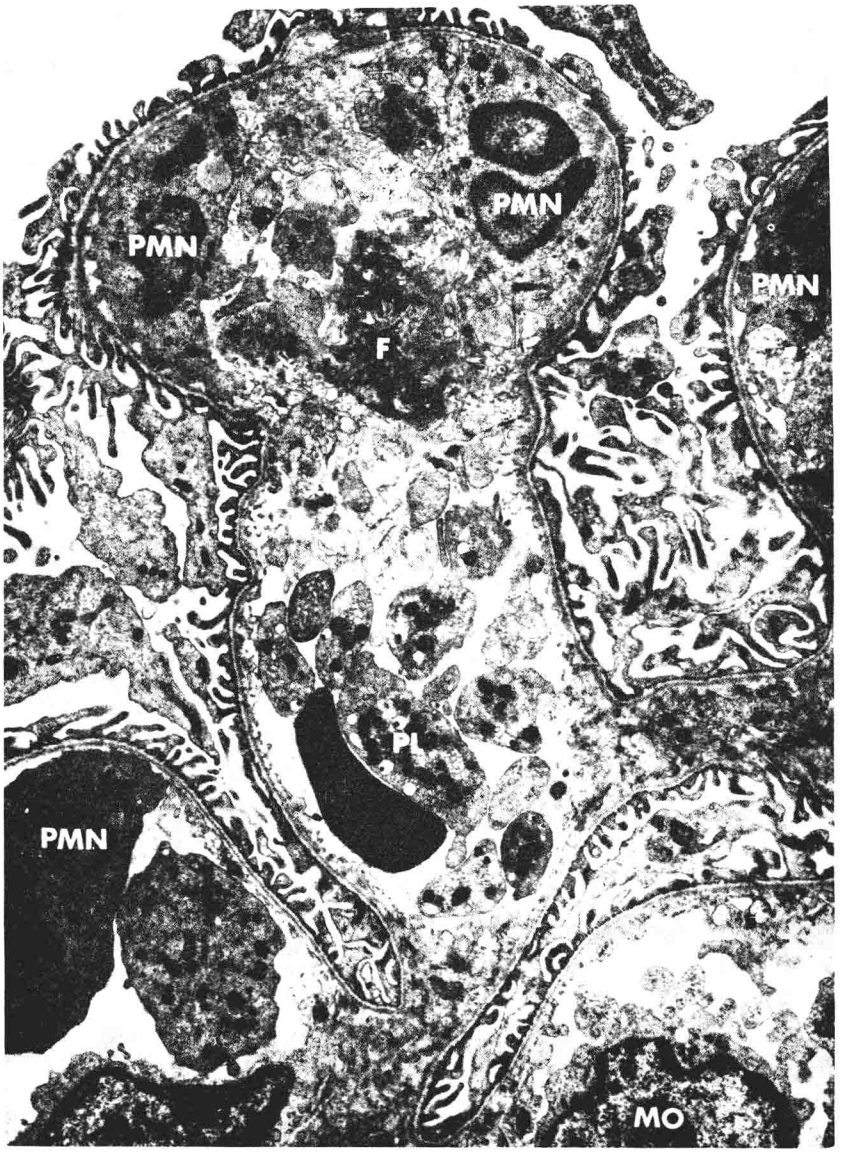


Fig. 3. Glomerular lesions of rat Masugi nephritis 2 hrs after injection with nephrotoxic rabbit IgG. The capillary lumens are occluded by leukocytes (PMN), fibrin (F), platelets (PL), and a monocyte (MO). PMNs show direct contact with basement membranes. ×5600. [H. SHIGEMATSU, Virchows Arch. Abt. B 5, 187 (1970)]

severity of the glomerular injury. Migrant PMNs exhibit direct contact with the denuded GBM or appear to be replacing the endothelium (COCHRANE *et al.*, 1965; SHIGEMATSU, 1970). Increased GBM permeability is suggested by the foot process fusion of podocytes. At 24 hours and thereafter PMNs disappear

from the capillary tufts but the lumen is again crowded with monocytes. Some monocytes are found to be closely attached to the GBM (SHIGEMATSU, 1970). These monocytes exhibit prominent phagocytic activities for fibrin or cell fragments and change into large macrophages or epithelioid cells. The monocytic accumulation is transient and the patency of the lumen is well restored within 72 hours. The denuded GBM is again covered by the endothelium. In this reparatory process, the participation of endothelial cells is reflected by increased numbers of cytoplasmic ribosomes and occasional mitotic figures. It has been confirmed in rats tolerant to rabbit IgG (FELDMAN *et al.*, 1963) that the first phase is transient and that the original glomerular architecture is restored within a few weeks.

On the other hand, marked thrombotic changes can be induced by the administration of a large dose of rabbit NTAbs (UNANUE *et al.*, 1968). Under this condition, the migrant cell accumulation is not prominent and the glomerular capillary lumens are diffusely occluded by fibrin or fibrinoid material. Such exaggerated thrombotic lesions terminate in diffuse necrosis of the renal parenchyma and rapid uremic death of the diseased animals.

It has been suggested that the first phase of rat Masugi nephritis depends largely upon the participation of serum complement (HAMMER and DIXON, 1963; BAXTER and SMALL, 1963) and of PMNs mediated by the complement fixation (COCHRANE *et al.*, 1965). In fact, glomerular changes are significantly modified in an experimental system in which there is little or no participation of complement. In rat Masugi nephritis produced by nephrotoxic guinea pig IgG_1 which did not fix complement *in vitro* at all but did so a little *in vivo*, endothelial exfoliation and fibrin deposition were detectable, but accumulation of PMNs was minimal (KOBAYASHI *et al.*, 1973a). $F(ab')_2$ fragments obtained from the nephrotoxic IgG_1 only caused endothelial exfoliation (KOBAYASHI *et al.*, 1973b). Moreover, it was reported that in congenitally complement deficient mice, NTAbs caused only a very mild glomerular disease in which leukocytic infiltration and proliferative change did not take place (UNANUE *et al.*, 1967b).

b) The Second Phase of Masugi Nephritis

The second phase develops several days after injection of NTAbs and is consistent with the appearance of autologous antibody (KAY, 1940). The autologous antibody specifically reacts with antigen (NTAb) fixed previously on the GBM so that its distribution is basically identical to that of antigen (ORTEGA and MELLORS, 1956; SEEGAL *et al.*, 1963). Thus, in this phase, the host antibody is visualized by immunofluorescence as a continuous linear pattern. Simultaneously, complement is also fixed in the glomeruli in a similar fashion (UNANUE and DIXON, 1964). The pathologic changes in the second phase might be greatly modified by a number of factors such as animal species, the nature and amounts of NTAbs injected, and the intensity of host immune responses. In rat Masugi nephritis the kidney damage in the second phase is

usually progressive, undergoing a chronic glomerular disease probably due to the continuing production of host antibody and its fixation to antigen (rabbit NTAb). This is in sharp contrast to the transient glomerular injury in the first phase as was proved in rats that were tolerant to rabbit IgG (HAMMER and DIXON, 1963; FELDMAN *et al.*, 1963).

Ultrastructurally, the predominant change in the second phase is the appearance of dense granular subendothelial deposits intimately applied to the GBM (FELDMAN, 1963; FELDMAN *et al.*, 1963). Endothelial cells are swollen and mesangial cells increase in numbers (SUZUKI *et al.*, 1963). In a more chronic stage the mesangium is conspicuously widened due to an increase of the cellular elements as well as the basement membrane-like material or ground substance containing collagen fibers (SUZUKI *et al.*, 1963). The GBM is progressively thickened, apparently by incorporation of the subendothelial deposits (FELDMAN, 1963). The basement membrane-like material then appears in the lumen, irregularly separating the intracapillary cells. These processes may terminate in the virtual obliteration of the capillary tufts with destruction of the glomerular architecture.

An attempt has been made to clarify glomerular events limited to the second phase by using a weak rabbit NTAb that is not capable of inducing the first phase (SHIGEMATSU and KOBAYASHI, 1971). The results obtained so far again confirm that the major change in the secondary phase is the GBM thickening with dense deposits. There were mild proliferative changes caused by intraluminal or subendothelial accumulation of migrant monocytes. The deposits were mostly observed at the subendothelial aspect of the GBM but some were also present at the outer aspect. With fluorescent microscopy, the subepithelial deposits were discernible as a granule located at the outer surface of linear fluorescence.

As compared to rat Masugi nephritis, a more severe, proliferative glomerular injury is seen in rabbit Masugi nephritis. It seems that this rabbit glomerulonephritis can serve as an excellent model for analyzing the nature of proliferative glomerular changes. Therefore, its pathologic features will be described below in some detail.

The second phase can be induced in rabbits without the preceding first phase by injection with an appropriate amount of duck NTAbs. The glomerulonephritis becomes manifest after a latent period of several days, and, within a month, a resolution occurs if the glomeruli have not been severely damaged. The GBM shows swelling and thickening, and appears somewhat porous because of its decreased density (SAKAGUCHI *et al.*, 1957). Electron dense or opaque deposits are present at the subendothelial side of the GBM. The mesangial matrix is edematous and becomes inhomogeneous. These changes are often associated with the detachment of the endothelium from the GBM (SAKAGUCHI *et al.*, 1957; KONDO and SHIGEMATSU, 1972).

The second step of the process is characterized by marked glomerular hypercellularity. Obviously both endothelial cells and mesangial cells contrib-

ute in varying degrees to the proliferative glomerular change (SAKAGUCHI *et al.*, 1957; FUJIMOTO *et al.*, 1964). These fixed cells are swollen, proliferated, and their organelles are either enlarged or increased in number. However, with regard to the origin of increased mononuclear cells in the affected glomeruli, the progressive accumulation of migrant monocytes is more important (KONDO and SHIGEMATSU, 1972). Of particular note is that these monocytes show a remarkable tendency to contact intimately with the GBM. Their phagocytic activities are also prominent. Furthermore, a series of transformations of monocytes into macrophages, epithelioid cells, and occasional multinucleated giant cells is seen. Infiltration of PMNs is variable. Platelets, fibrin, or other thrombotic materials are seen occasionally in the lumen. As mentioned above, the proliferation of the fixed glomerular cells is important, yet it is not a major factor contributing to the hypercellularity. Therefore, the disappearance of migrant monocytes is principally followed by a resolution of the glomerular changes without severe structural alterations (KONDO and SHIGEMATSU, 1972). However, a thickening of the mesangium may persist for several months.

In contrast, rapidly progressive glomerulonephritis with a marked structural distortion is seen in rabbits receiving a larger amount of duck NTAbs (KONDO *et al.*, 1972). It seems that such a disorganizing glomerulonephritis is initiated by a conspicuous loosening of the mesangial matrix and the GBM. The mesangium is widened due to extensive edematous swelling or lysis of the matrix and hypertrophy as well as a proliferation of mesangial cells. There are local proliferations of endothelial cells and an enhanced accumulation of monocytic cells which are located in the capillary lumen, subendothelial space, and loosened mesangium. The tufts are frequently occluded by fibrin or fibrinoid substances and PMNs. The significance of mesangiolysis is a loss of the supporting element of the glomerular tuft structure which is then followed by an accentuation of lobular appearance in a mild case and, in an advanced stage, bollooning or globular transformation of the tufts. In fact, in a severely affected glomerulus, neither the mesangium nor the capillary lumen can be discerned, and the tufts are transformed into a dilated sack filled with numerous monocytes, proliferated glomerular cells (mostly mesangial cells), thrombotic material, and PMNs. Under these conditions, the GBM becomes progressively thinner and extended, eventually resulting in local or diffuse rupture. Owing to the GBM rupture a massive influx of monocytes or other blood elements occurs in Bowman's space. Although both visceral and parietal epithelial cells are involved in the process and damaged, their reactive overgrowth soon becomes evident. The extracapillary inflammation thus leads to formation of the crescent composed of monocytic cells and proliferated epithelial cells (KONDO *et al.*, 1972).

Little is known about mediators involved in the initiation and/or the persistence of the second phase, despite these remarkable histologic findings. It is unlikely from the morphologic aspect that PMNs again play a significant role as they do in the first phase of rat Masugi nephritis. The participation of complement is not *sine qua non*, although the disease process might be

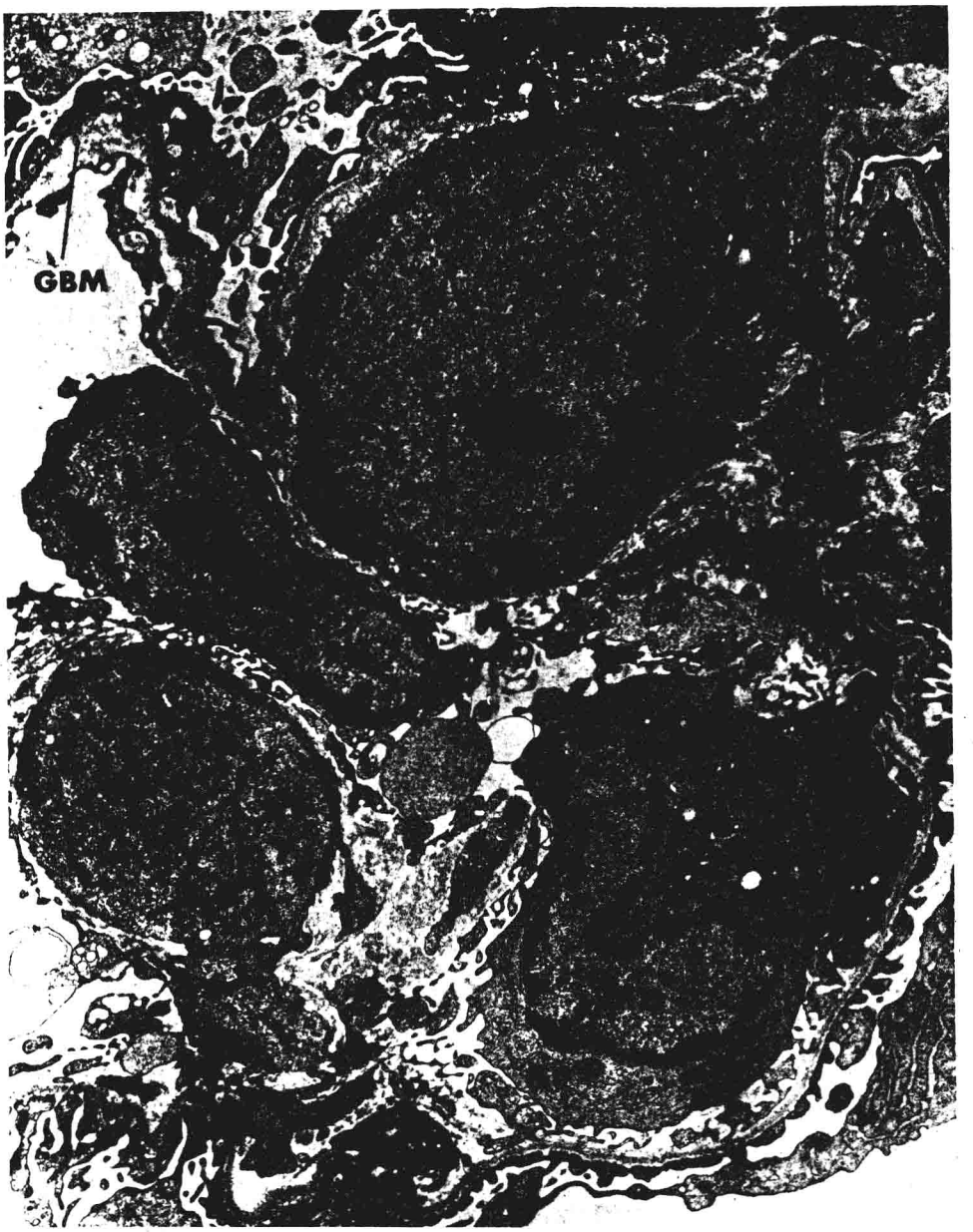


Fig. 4. An early glomerular change of rabbit Masugi nephritis induced by injection with nephrotoxic duck antibody (second phase). Marked swelling of mesangial cells (MS), a monocyte (MO) exhibiting localized contacts with basement membrane (arrow), and subendothelial mottling of basement membrane (GBM) are seen. EN: endothelial cell. ×8600

modified in complement deficient animals (UNANUE *et al.*, 1967b). Of the many possible mediators accounting for the pathogenesis, the most outstanding is the coagulation process. There is evidence that coagulation apparently

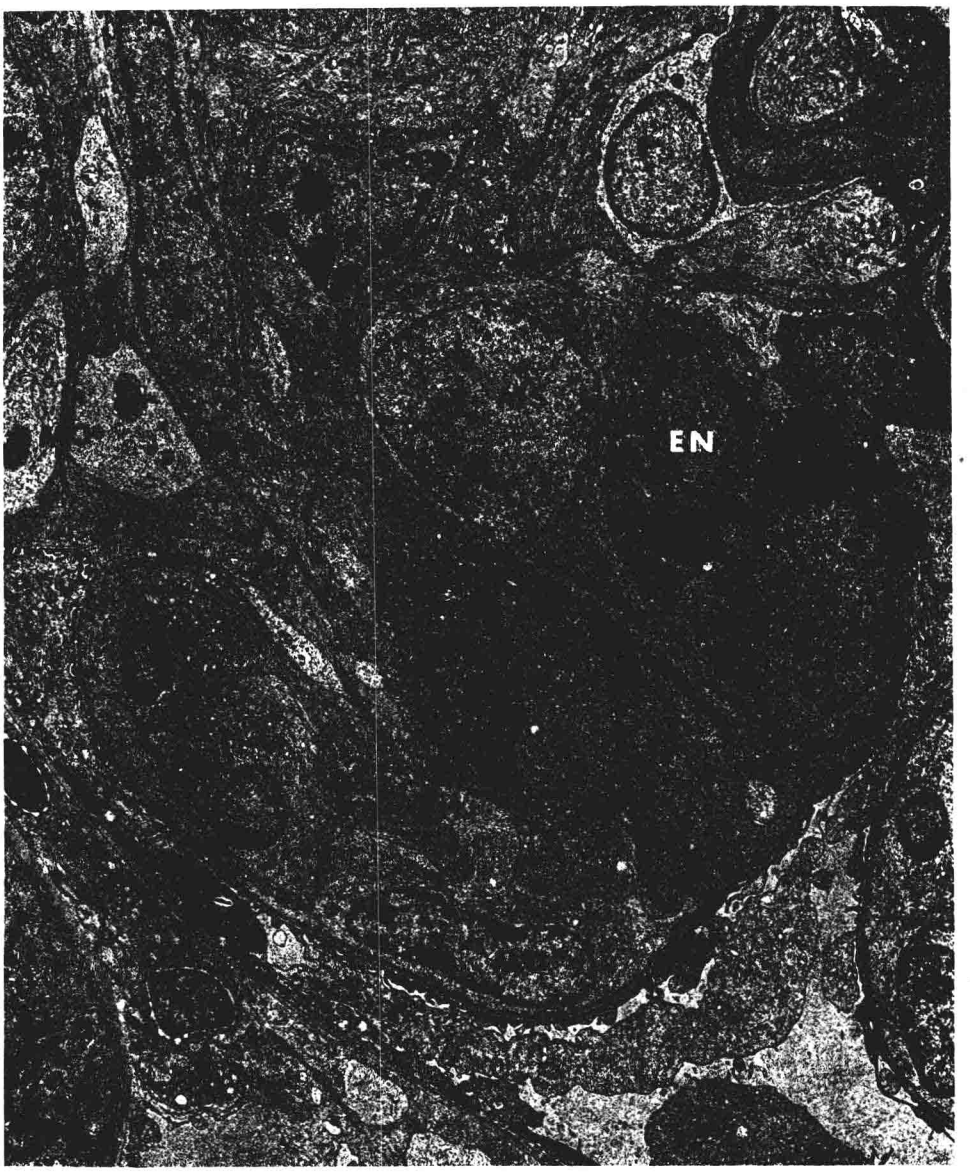


Fig. 5. Rabbit Masugi nephritis induced by injection with nephrotoxic duck antibody (second phase). Note a balloon-like distortion of a tuft filled with numerous monocytic cells (MO) and some swollen mesangial cells (MS), and endothelial cells (EN). ×4100

contributes to glomerular lesions in rabbit Masugi nephritis induced by a potent sheep NTAb (VASALLI and MCCLUSKEY, 1964). About 5 days after injection of this sheep NTAb, a definite proliferation of endothelial and mesangial cells (intracapillary cells) developed, often associated with deposits of material with staining properties of fibrin. Fibrin and fibrinoid material

were also seen in Bowman's space where they were invaded by proliferating epithelial cells (crescent formation). In contrast, it was found that these changes could be prevented strikingly, if the animals were treated with anticoagulant (warfarin).

Ultrastructural analysis of Masugi nephritis has been performed in other animal species. In dogs injected with rabbit or sheep NTAb, the first phase was characterized by a "quellung" and occasional longitudinal splitting of the GBM, whereas in the second phase there was proliferation of intracapillary cells with a deposition of electron dense material between the endothelium and the GBM, and between the proliferated intracapillary cells (MOVAT *et al.*, 1961). In the monkey, a proliferative glomerulonephritis appeared 6–10 days after injection of rabbit NTAb. Progressive basement membrane irregularities including thickening, splitting, and focal defects were observed, together with proliferations of endothelial, mesangial, and epithelial cells (BATTIFORA and MARKOWITZ, 1969).

2. Steblay Nephritis

Autologous antibodies with a nephritogenic property (autologous anti-GBM antibody) could be produced in some species of animals through immunization with homologous or heterologous GBM antigens. The sheep is particularly susceptible and fulminant glomerulonephritis is manifested within several months by repeated injections of human or other heterologous GBM antigens in Freund's complete adjuvant (STEBLAY, 1962). The antibody is localized linearly along the GBM as seen in immunofluorescence, and is capable of inducing glomerular injuries passively in the same species of animals, thereby indicating the autoimmune nature of the disease (LERNER and DIXON, 1966). Antibodies eluted from the GBM of nephritic sheep react, *in vitro*, with sheep GBM. They also react with lamb GBM *in vivo*, fix C3, and induce immediate glomerular injury (STEBLAY and RUDOFSKY, 1968). In the sheep or goat the glomerular lesions resulting in progressive renal failure are of a generalized crescentic type. Before the formation of fulminant crescents, characteristic GBM alterations are noted by electron microscopy (GERMUTH *et al.*, 1972b; OHNUKI, 1975). The GBM shows irregular thickening and increased density, becomes tortuous, and terminates in its rupture. Such serious GBM damage is accompanied by a massive exudation of blood elements into Bowman's space. It seems that crescentic epithelial proliferation involving both visceral and parietal epithelium is partly stimulated by increased GBM permeability (proteinuria) but more intensely by the influx of red cells, PMNs, monocytes, and fibrin in the extracapillary space through the GBM break. Between the proliferated epithelial cells, basement membrane-like material may soon appear and the cell clusters undergo fibroepithelial crescents (STEBLAY, 1962). In contrast, intracapillary changes are not remarkable and no dense deposits have been detected so far (MUEHRCKE *et al.*, 1967). Various glomerular alterations were also elicited in other animal species by similar procedures