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Mesangiolysis in diabetic glomeruli: Its role in the formation of nodular lesions

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Mesangiolysis in diabetic glomeruli: Its role in the formation of nodular lesions. In order to elucidate a participation of the mesangiolysis in the formation of diabetic nodular lesions, 355 kidney specimens obtained from 327 patients with primary diabetes mellitus were studied. Mesangiolyses begun by focal and segmental disintegration of the pivotal structure of the mesangium ("torn off phase"), resulting in cystic or aneurysmal dilatation of the involved tuft, were found in 56 specimens (16%). The dilated tufts were filled with lysed mesangial matrix, which showed a reticular or fibrillar arrangement ("structureless phase"), being followed by a concentrical re-arrangement ("reconstructive phase") and by the ultimate formation of diabetic nodules. The mesangiolysis of various phases was frequently found concomitant with severe diabetic arteriolosclerosis and, in the reconstructive phase, the lysed mesangial matrix near the recanalized capillary along the inner aspect of glomerular basement membrane was observed to be rearranged in a layered structure. These results suggest the hypothesis that: 1) the mesangiolysis is the initial lesion occurring in glomeruli in the process of diabetic nodule formation, and disturbed blood flow into glomeruli, caused by diabetic arteriolosclerosis, may be implicated in the development of the mesangiolysis; and 2) concentric compression of the lysed mesangial matrix by recanalized capillaries forms layered structures and ultimate completed diabetic nodules.

Nodular, diffuse and exudative lesions as well as diabetic arteriolosclerosis accompanied by hyalin deposition have been widely accepted as lesions characteristic to diabetic nephropathy. As a mechanism of nodule formation, extension of the diffuse lesion to the periphery of the tuft has been postulated [1–3], but Bloodworth [4] pointed out the possibility of organization of intra-glomerular microaneurysms, which were initially developed by the detachment of the so-called "anchor point" of the mesangial matrix. In addition, we have found that mesangiolyses were noted frequently along with nodular lesions or intra-glomerular microaneurysms. It suggests the strong possibility that mesangiolyses play an important role in the process of nodule formation; especially as the initial event. Thus, in this study, firstly the characteristics of the mesangiolysis observed in diabetic kidneys are described in detail, and secondly, the cause and role of mesangiolysis in the process of formation of nodular lesions is discussed.

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Methods

Patient population

Three hundred and fifty-five kidney specimens (342 biopsy and 13 autopsy specimens) obtained from 327 patients with diabetes mellitus were studied at the Kanazawa University Hospital between 1962 and 1984. This group was comprised of 201 men and 126 women diagnosed as insulin-dependent (IDDM) in 42 and non-insulin-dependent diabetes mellitus (NIDDM) in 285 patients. Patients with underlying diseases such as metabolic disease, liver disease, pancreatitis, steroid-induced glucose intolerance, primary or secondary renal disease except for diabetic nephropathy were excluded from this study.

At the time of histological examination, their ages ranged from 15 to 77 years (mean, 49.9 years; median, 51.8 years), and the duration of diabetes mellitus defined as the time between apparent clinical onset of diabetes mellitus and renal biopsy or autopsy ranged from 0.1 to 33 years (mean and median, 6.2 years and 4.6 years; 8.5 years and 3.8 years in IDDM; 5.8 years and 4.7 years in NIDDM, respectively). Urinary protein up to 9.8 g per day (mean, 2.3 g/day; median, 0.7 g/day) was persistently detected in 123 patients. Ninety patients had hypertension higher than 160 mm Hg in systolic and/or 95 mm Hg in diastolic. Glomerular filtration rate measured using sodium thiosulphate was less than 70 ml/min in 68 patients containing 16 less than 30 ml/min.

Histological examination

Kidney specimens fixed in 10% buffered formalin (pH 7.2), embedded in paraffin, cut at 3 μm and stained with hematoxylin and eosin, periodic acid Schiff's reagent (PAS), periodic acid silver methenamine (PAM) and Mallory-azan were observed under a light microscope. Each specimen contained nine or more glomeruli. We especially laid stress on those specimens stained with the PAM and PAS. The severity of the diffuse lesions was graded on a scale of 0 to IV according to the description by Gellman et al [5], and the severity of the arteriolosclerosis according to hyalin deposits as follows: grade 0, not noted; grade I, noted, but less than half around the arteriole; grade II, noted more than half around the arteriole; and grade III, noted all around the arteriole. Intra-glomerular microaneurysms were defined as dilatations of the tuft caused by the loss of holding of the capillaries or by disruption in the

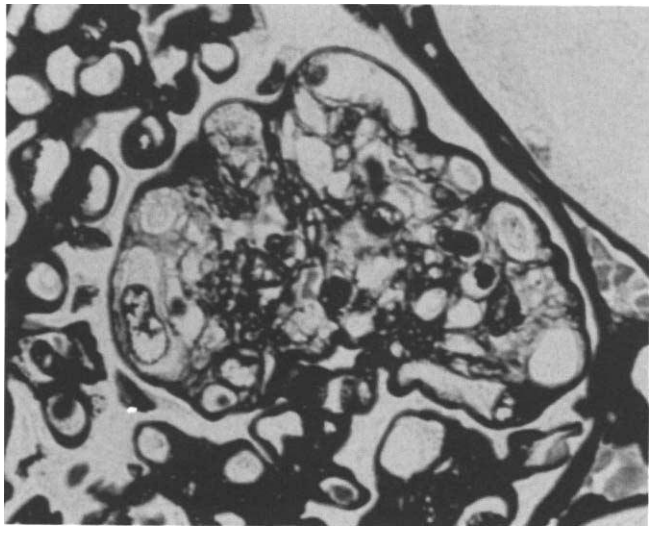

Fig. 1. *Light micrograph of mesangiolysis in the torn off phase.* Mesangial matrix in the central portion of the involved tuft shows loosening and disintegration, whereas the essential structure remains rather intact especially in the periphery of the tuft. PAM; × 1,600.

axial or stalk portion of the mesangium. Simple enlargements of single capillary lumen were excluded.

Nodular lesions, intra-glomerular microaneurysms and mesangiolyses were simply shown as to whether they were present or not in each specimen.

Other portions of 34 kidney specimens, which had any of mesangiolysis, microaneurysm or nodular lesions by light microscopy were pre-fixed with 2.5% glutaraldehyde in cocadylate buffer, and post-fixed with 2% osmium tetroxide (pH 7.2). After dehydration in an ethanol series, they were embedded in Epon 812. Ultrathin sections were stained with lead citrate and uranyl acetate, and were observed under an electron microscope (Hitachi HU-11).

Statistical analysis

Statistical analysis was performed by ordinary chi-square test with correction by Yates' component. For the analysis of the relation between prevalence of mesangiolysis, microaneurysm or nodular lesion and the severity of diabetic diffuse lesion or arteriolosclerosis, Cochran's regression chi-square test [6] and Wilcoxon's rank sum test were used. The statistical significance was defined as P value less than 0.05.

Results

Light and electron microscopic findings of mesangiolysis

Mesangiolyses were light microscopically observed in 56 specimens as lesions of a spectrum from disintegration of the mesangial structure to nodule formation (Figs. 1, 2, 3). The disintegration initially appeared as focal and segmental dissociation of the pivotal structure of the mesangium, followed by cystic dilatation of the involved tuft. The dilated tufts were filled with dissociated mesangial matrix, which, thereafter, re-arranged concentrically forming a diabetic nodule. Precise pathological changes were as follows.

Mesangial matrix. As a process of mesangiolysis, "torn off phase", "structureless phase", "reconstructive phase" and a phase of completion of nodule formation, characterized by the appearance of mesangial matrix in the involved tufts, were observed.

Torn off phase. The mesangial matrix, especially in the central pivotal portion, was loosened and partially torn off, resulting in centrifugal dilatation of the involved tuft, whereas in the periphery of the tuft the essential structure of the mesangium remained rather intact (Fig. 1). In the rarefied mesangial area, stranded and electron-dense material regarded as mesangial matriceal debris were seen by electron microscopy, and the anchoring of the mesangium to the glomerular basement membrane was scarcely involved (Fig. 4). Such lesions were found in two out of the 56 specimens with the mesangiolysis.

Structureless phase. Dissociation of the mesangial matrix extended to the whole tuft, including anchor points [4]. The involved tuft showed aneurysmal cystic dilatation, the inside of which was occupied by the PAM-positive matrix appearing as a fibrillar or reticular network (Fig. 2). Ultrastructural examinations showed this network consisted of the same stranded and electron-dense material as seen in the "torn off phase" (Fig. 5). The anchor points were often completely dissociated (Fig. 6). These lesions were observed in five specimens.

Reconstructive phase. The mesangial matrix, re-arranging concentrically to the central portion of the involved tuft, formed a rough concentric and layered structure in consequence of compression by glomerular capillaries, which were recanalized in the periphery of the tuft (Fig. 3). However, the layered structure was not tight with irregular and obscure margins. Ultrastructural observation revealed the material observed in the "structureless phase" had a layered appearance. The layers tended to be compacted near the central portion of the tuft (Fig. 7).

Completion of nodule formation. The mesangial matrix was tightly compacted and layered, showing a typical diabetic nodule (Fig. 8).

Growth of nodule. In some nodules, apparently new layers were observed around old ones (Fig. 9).

Glomerular capillaries. Throughout the whole process of the mesangiolysis, the continuity of the glomerular basement membrane (GBM), defined as PAM-positive capillary wall by light microscopy, was maintained relatively well. In the "torn off phase" the capillaries were dislocated to the periphery of the dilated tuft, but their essential structure was maintained, showing patent lumina (Fig. 1), the inside of which was covered with endothelial cells (Fig. 4).

However, in the "structureless phase" only a few capillaries of various sizes covered with swollen endothelial cells were recognized in the reticular or fibrillar network of mesangial matrix (Fig. 2).

In the "reconstructive phase", recanalized capillaries, occasionally indistinguishable from the microaneurysm, were observed between the network and GBM (Fig. 3). GBM was attenuated irregularly, and, in some glomeruli, red blood cells were extravasated into the network or Bowman's space (Fig. 3A).

Even after completion of nodule formation, microaneurysms

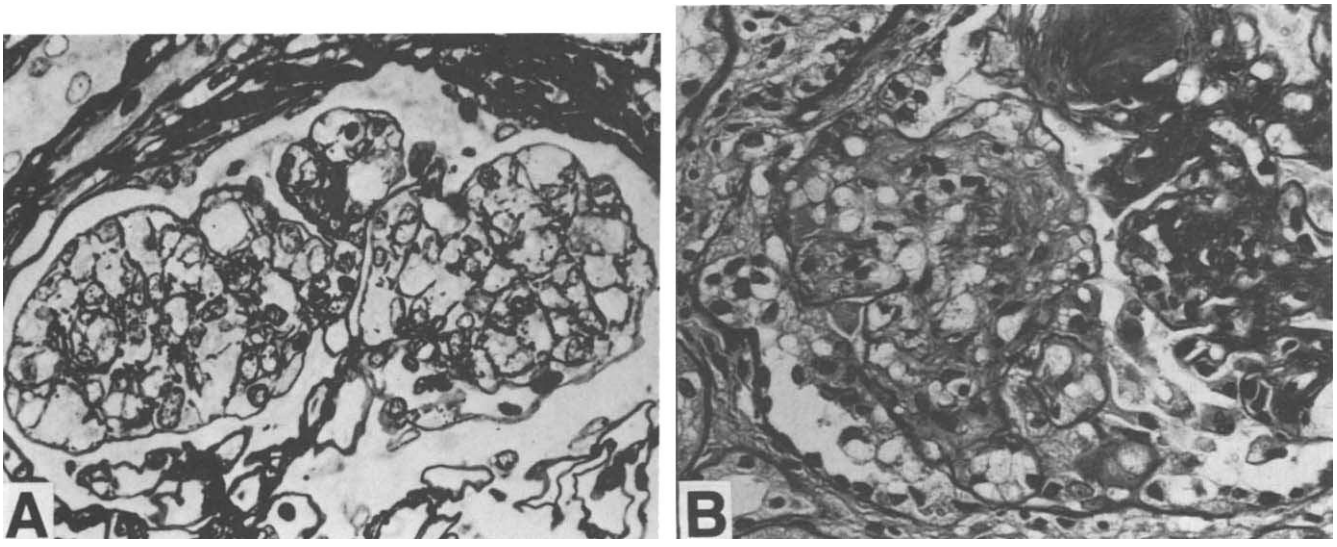

Fig. 2. *Light micrograph of mesangiolysis in the structureless phase.* Disintegration of mesangial matrix extends to the whole tuft. **A.** PAM; × 650. **B.** PAS; × 400.

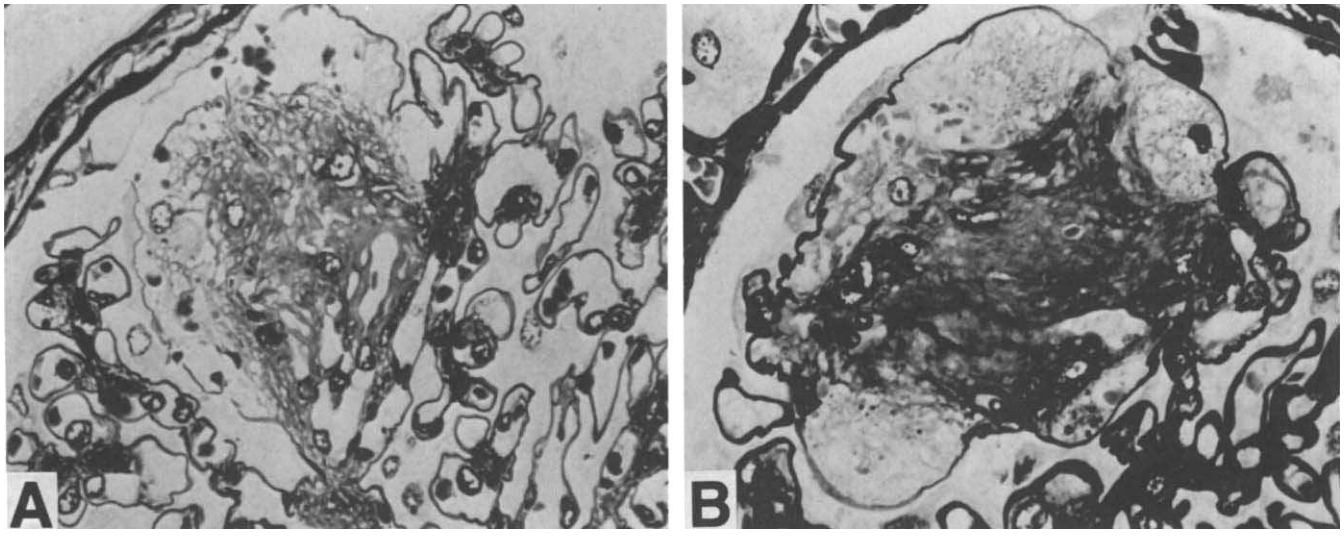

Fig. 3. *Light micrograph of mesangiolysis in the reconstructive phase.* **A.** The mesangial matrix, appearing as a reticular network, is seen concentrated in the central part of the tuft, showing rough layered structure. PAM; × 800. **B.** The concentrated fibrillar network showing a tendency of fusion resembles the diabetic nodular lesion. PAM; × 800.

or capillaries with flat lumina remained (Fig. 8), whereas GBM showed nearly normal thickness.

Cell components. Throughout the whole process of the mesangiolysis, some glomerular cells showed swelling and vacuolar change, and these changes were most pronounced in the structureless phase. However, the number of cells decreased in the reconstructive phase and in completed nodules.

Prevalence of the glomerular lesions

The mesangiolysis, microaneurysm and nodular lesion were noted in 56 (16%), 60 (17%) and 66 (19%) out of the 355 specimens observed, respectively (Fig. 10), and 44 specimens had each of these three lesions simultaneously. The prevalence of the microaneurysm was significantly higher in specimens with the mesangiolysis (51 of 56) compared to those without (9 of 299, $P < 0.001$). Nodular lesions were also found more frequently in specimens with the mesangiolysis (48 of 56) than those without (18 of 299, $P < 0.001$), whereas among the 299 specimens without, 278 (93%) had neither microaneurysm nor nodular lesion.

The prevalence of the mesangiolysis, microaneurysm and nodular lesion in specimens of IDDM was 18%, 18% and 22%, and of NIDDM 15%, 17% and 18%, respectively (no statistical significance).

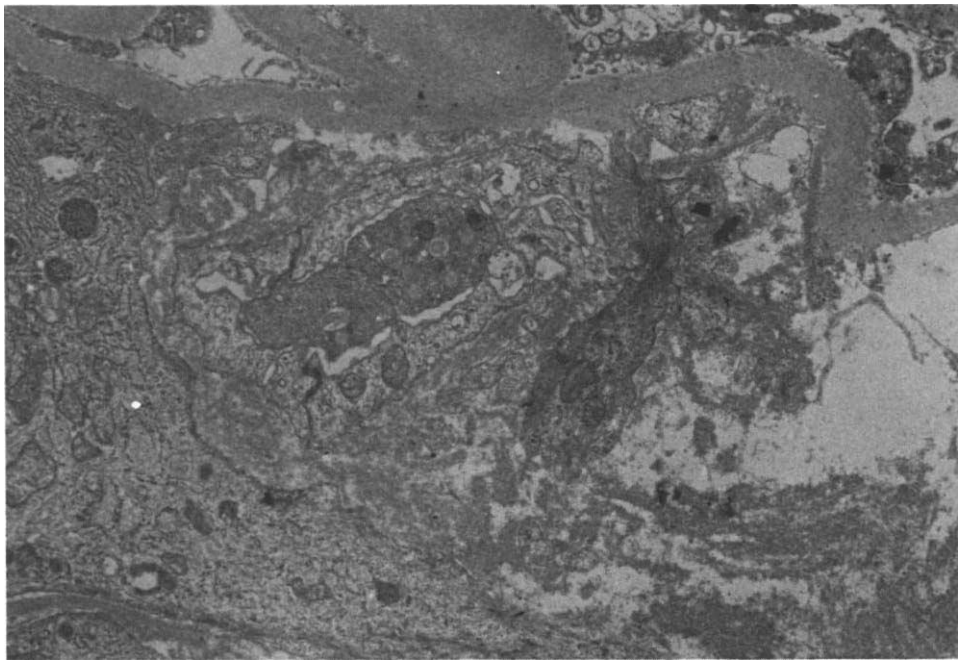

Fig. 4. *Electron micrograph of the mesangiolysis in the torn off phase.* The mesangial matrix appears to be rarefied. The capillary covered by the endothelial cells is missing its hold by the mesangial matrix. The glomerular basement membrane barely anchors to the mesangium. × 8,200.

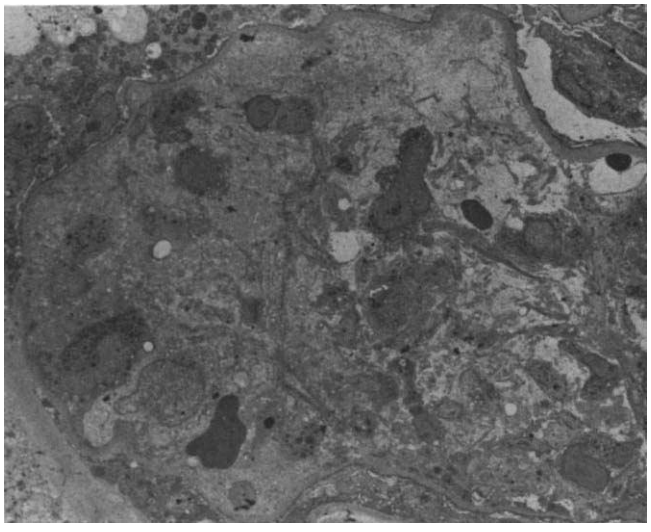

Fig. 5. *Electron micrograph of the mesangiolysis in the structureless phase.* The stranded material regarded as mesangial matriceal debris occupies the dilated tuft. The anchor points of the mesangial matrix to the glomerular basement membrane are disrupted. × 1,500.

Relation between diffuse lesion or diabetic arteriolosclerosis and mesangiolysis

As the grade of the diffuse lesion and of arteriolosclerosis advanced, the prevalence of the mesangiolysis became significantly higher (Tables 1 and 2, $P < 0.001$ for each). No specimen with the mesangiolysis showed grade 0 of arteriolosclerosis, and only two specimens (4%) showed grade I. The remaining 54 specimens (96%) showed more than grade II arteriolosclerosis. All five specimens with the mesangiolysis and only mild diffuse lesions up to grade I had severe arteriolosclerosis; grade III appeared in four and grade II in one specimen.

The prevalence of the microaneurysm and nodular lesions showed a similar tendency to that of the mesangiolysis (Tables 1 and 2), but the latter was not detected in cases of grade 0 or I diffuse lesions.

There were eight specimens with no nodular lesions but with the mesangiolysis. The severity of their diffuse lesion was significantly milder than those of the specimens with the nodular lesion and mesangiolysis (Table 3), whereas the arteriolosclerosis was as severe as grade II to III, as observed in most patients with both nodular lesion and mesangiolysis (Table 4).

Discussion

Expansion of the diffuse lesion to the periphery of the glomerular tuft has been widely accepted [1–3] as a possible explanation of nodule formation in diabetic kidneys. However, Bloodworth [4] pointed out the possibility that the large nodules were formed by the organization of glomerular capillary microaneurysms caused by disruption of so-called anchor points, and he suggested, "some unknown injury or stimulus caused the disruption of anchor points".

In addition, in this study we observed the mesangiolysis exhibiting a loosening and dissociation of the mesangial matrix in the central portion of the glomerular tuft, which might be an initial lesion, and extension of the lesion to the whole tuft including anchor points, showing disruption of anchor points, cystic dilatation of the involved tuft, fibrillar or reticular arrangement of the mesangial matrix therein, and concentric and layering re-arrangement of the matrix together with diabetic nodules.

Incidentally, it has been explained that in experimental animals mesangiolysis can be caused by intravenous administration of Habu snake venom [7–10] or of anti-thymocyte serum [11], and injection of croton oil into the renal artery [12]. Apart

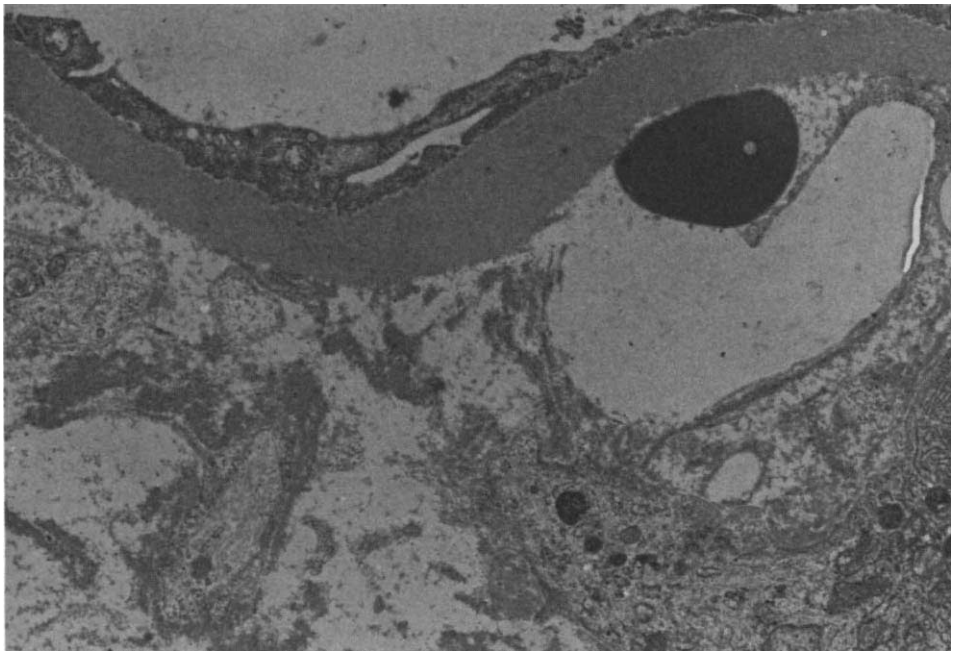

Fig. 6. *Electron micrograph of the mesangiolysis in the structureless phase.* Disruption of anchor point and burst of capillary lumen are seen. × 8,300.

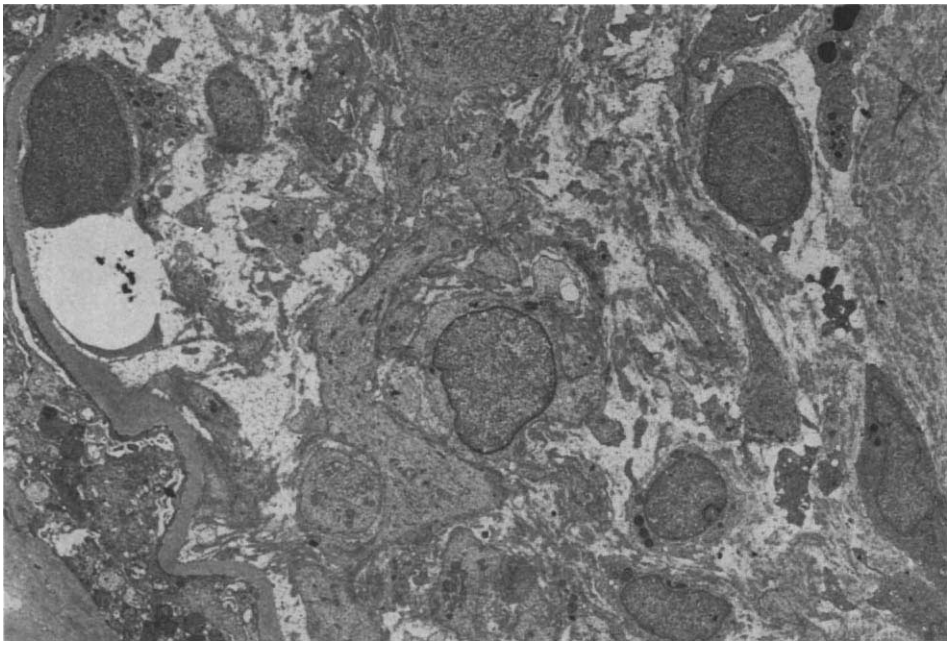

Fig. 7. *Electron micrograph of the mesangiolysis in the re-constructive phase.* The matriceal debris tend to distribute concentrically and form layers near the central portion of the tuft. × 2,800.

from administration of these foreign materials, Sheehan and Davis [13, 14] reported that mesangiolyses developed after transient interruption of renal blood flow and following good re-flow in rabbits.

In addition, the prevalence of the mesangiolysis, in this study, significantly increased in specimens with more severe arteriolosclerosis, indicating the possibility that altered blood flow, probably ischemia in the glomerulus caused by arteriolosclerosis, participates in the development of the mesangiolysis in diabetic glomeruli. Furthermore, five specimens showing the mesangiolysis and moderate to severe arteriolosclerosis concomitant with only mild (grade 0 or I) diffuse lesions also support that possibility rather than a participation of the diffuse lesion by itself.

Concerning the process of nodule formation following mesangiolysis, it was postulated that, as shown in Figure 3B, it is formed by the compression of fibrillar or reticular mesangial matrix concentrically toward the central portion of the tuft by recanalized capillaries in the marginal part of the tuft. In fact, we observed the concentrically layered structure only beside

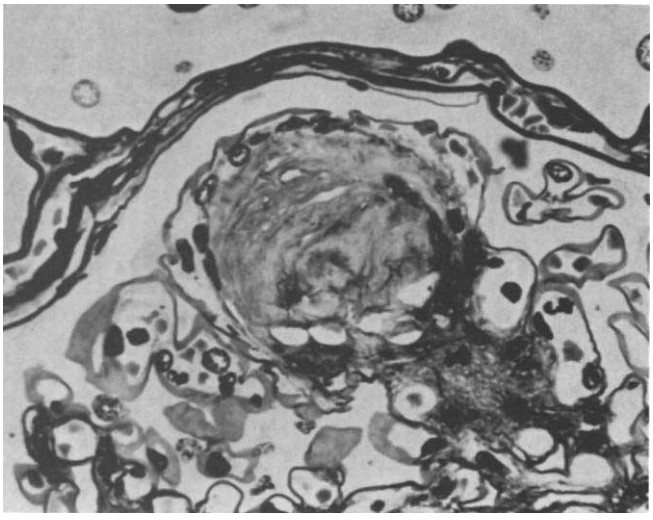

Fig. 8. *Light micrograph of a completed nodular lesion.* PAM; × 800.

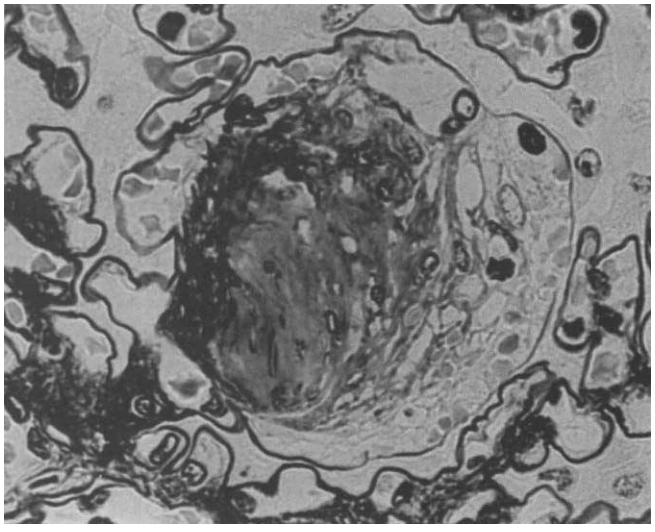

Fig. 9. *Light micrograph of a growing nodular lesion.* New loose layers are seen around the old tight nodule. PAM; × 1,200.

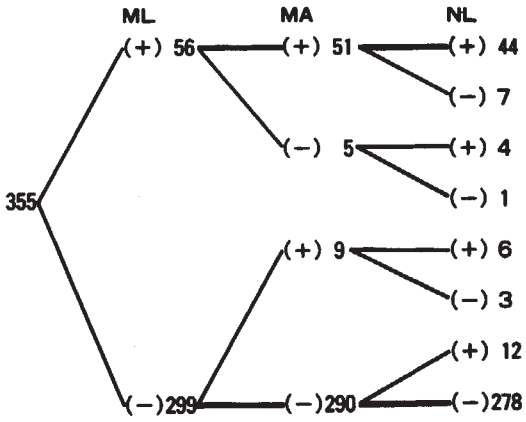

Fig. 10. *Prevalence of various diabetic glomerular lesions.* ML, mesangiolysis; MA, microaneurysm; NL, nodular lesion.

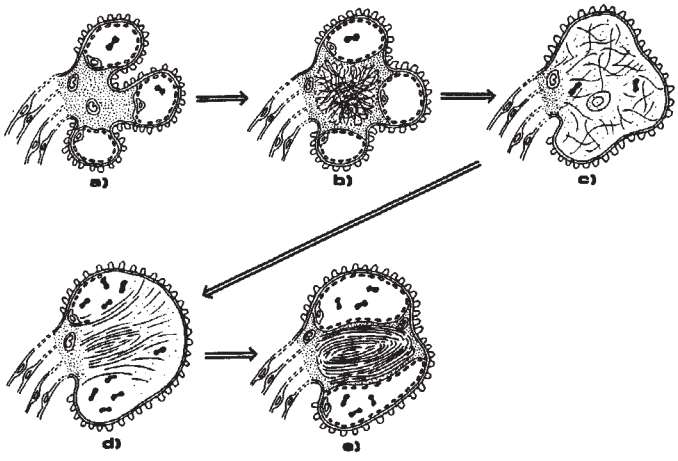

Fig. 11. *Hypothetic schema of morphogenesis of diabetic nodular lesions.* a) A tuft with diabetic diffuse lesions. b) Loosening and disintegration of mesangial matrix (torn off phase). c) A dilated tuft occupied by reticulated mesangial matrix (structureless phase). d) Concentrated matrix showing layered structure (reconstructive phase). e) Completed diabetic nodule.

the recanalized capillaries (Fig. 3B). This may be a reason why diabetic nodules, especially ones not fully developed, are not necessarily round.

Incidentally, it was described that the mesangiolyses observed in the aforementioned non-diabetic kidneys were accompanied by segmental cellular proliferation [7, 8, 11, 14] and hyalinization [8], but not followed by nodule formation, being distinctly different from mesangiolyses seen in diabetic kidneys.

As diseases producing diabetic nodule-like lesions, myeloma kidney [15–17], light chain renal disease [18], lobular glomerulonephritis [17, 19], renal amyloidosis [17, 20, 21], membranoproliferative glomerulonephritis [22] and carbon disulfide nephropathy [23] have been known. Experimentally similar lesions also develop in rabbits with hypercholesterolemia [24, 25]. Among these glomeruli essentials for nodule formation are the coexistence of increased mesangial matrix or deposition of disease-related material in the mesangium. In our diabetic cases, mesangiolyses were noted even in patients with grade 0 to I of diffuse lesions, but no nodular lesions. Based on these data, it is postulated that the presence of moderate to severe diffuse lesions is essential for transformation of the mesangiolysis to the nodular lesion, during which the increased mesangial matrix supplies enough material for nodule formation.

Summarizing the above process, a course as shown in Figure 11 seems to follow the appearance of the mesangiolysis; when ischemia works to a glomerulus already involved by moderate to severe diffuse lesions (Fig. 11A), the increased mesangial matrix is loosened and dissociated at the central pivotal portion of the tuft (Fig. 11B, torn off phase). By the dissociation of the mesangial matrix extending to the whole tuft, it appears cystic and is occupied by fibrillar or reticular network (Fig. 11C, structureless phase). However, capillaries recanalized in the periphery of the tuft compress the lysed mesangial matrix concentrically to form roughly layered structures (Fig. 11D, reconstructive phase), followed by tightening of the structure to

Table 1. Relationship between severity of diffuse lesions and prevalence of mesangiolysis, microaneurysm and nodular lesions

Grade of diffuse lesion		Mesangiolysis		Microaneurysm		Nodular lesion	
		N	(%)	*N*	(%)	*N*	(%)
0	(*N* = 98)	1	(1.0)	1	(1.0)	0	(0.0)
I	(*N* = 120)	4	(3.3)	4	(3.3)	0	(0.0)
II	(*N* = 71)	17	(23.9)	19	(26.8)	19	(26.8)
III	(*N* = 65)	33	(50.8)	35	(53.8)	46	(70.8)
IV	(*N* = 1)	1	(100.0)	1	(100.0)	1	(100.0)
χ^2		85.2		92.5		143.7	
$P(\chi^2)$		<0.001		<0.001		<0.001	

χ^2, chi-square for regression (d.f.=1), calculated by scoring as follows: grade 0, −3; grade I, −1; grade II, 1; and grade III +IV, 3.

Table 2. Relationship between severity of arteriolosclerosis and prevalence of mesangiolysis, microaneurysm and nodular lesions

Grade of arteriolosclerosis		Mesangiolysis		Microaneurysm		Nodular lesion	
		N	(%)	*N*	(%)	*N*	(%)
0	(*N* = 112)	0	(0.0)	0	(0.0)	0	(0.0)
I	(*N* = 109)	2	(1.8)	2	(1.8)	4	(3.7)
II	(*N* = 89)	28	(31.5)	32	(36.0)	38	(42.7)
III	(*N* = 45)	26	(57.8)	26	(57.8)	24	(53.3)
χ^2		98.4		102.0		97.0	
$P(\chi^2)$		<0.001		<0.001		<0.001	

χ^2, chi-square for regression (d.f.=1), calculated by scoring as follows: grade 0, −3; grade I, −1; grade II, 1; and grade III, 3.

Table 3. Relationship between diffuse lesions and nodular lesions in patients with mesangiolysis

Grade of diffuse lesion	Mesangiolysis without NL	Mesangiolysis with NL
0 (*N* = 1)	1	0
I (*N* = 4)	4	0
II (*N* = 17)	2	15
III (*N* = 33)	1	32
IV (*N* = 1)	0	1

Abbreviation is: NL, nodular lesion.

Statistical comparison was made by Wilcoxon's rank sum test; $P < 0.005$.

Table 4. Relationship between arteriolosclerosis and nodular lesions in patients with mesangiolysis

Grade of arteriolosclerosis	Mesangiolysis without NL	Mesangiolysis with NL
0 (*N* = 0)	0	0
I (*N* = 2)	0	2
II (*N* = 28)	4	24
III (*N* = 26)	4	22

Abbreviation is: NL, nodular lesion.

Statistical comparison was made by Wilcoxon's rank sum test; $P = 0.39$ (NS)

ultimately form nodular lesions (Fig. 11E, completion of nodule). A higher prevalence of the nodular lesion (19%) than the mesangiolysis (16%) seems to be explained by the postulation that the nodular lesion remains as it is when once formed, while the mesangiolysis appears transiently in the process of nodule formation. Especially the rarer findings of "torn off phase" and "structureless phase" may indicate that they transform to the "reconstructive phase" in a short time. Indeed, mesangiolyses caused by Habu snake venom in "early phases" might be the same lesions as those observed in "torn off phase" or "structureless phase" in this study; the lesions remain for only three to seven days after the administration of the venom [7, 8].

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References

1. Dachs S, Churg J, Mautner W, Grishman E: Diabetic nephropathy. *Am J Pathol* 44:155–168, 1977
2. Kimmelstiel P, Kim OJ, Beres J: Studies on renal biopsy specimens, with the aid of the electron microscope. I. Glomeruli in diabetes. *Am J Clin Pathol* 38:270–279, 1962
3. Suzuki Y, Churg J, Grishman E, Mautner W. Dachs S: The mesangium of the renal glomerulus; Electron microscopic studies of pathologic alterations. *Am J Pathol* 43:555–578, 1963
4. Bloodworth JMB Jr: A re-evaluation of diabetic glomerulosclerosis. 50 years after the discovery of insulin. *Human Pathol* 9:439–453, 1978
5. Gellman DD, Pirani CL, Soothill JF, Muehrcke RC, Kark RM: Diabetic nephropathy: A clinical and pathologic study based on renal biopsies. *Medicine* 38:321–367, 1959
6. Cochran WG: Some methods for strengthening the common χ^2 tests. *Biometrics* 10:417–451, 1954
7. Cattel V, Bradfield JWB: Focal mesangial proliferative glomerulonephritis in the rat caused by Habu snake venom. A morphologic study. *Am J Pathol* 87:511–524, 1977
8. Morita T, Kihara I, Oite T, Suzuki Y: Mesangiolysis. Sequential ultrastructural study of Habu venom-induced glomerular lesion. *Lab Invest* 38:94–102, 1978
9. Sakaguchi H, Kawamura S: Electron microscopic observations

of mesangiolysis: The toxic effects of the "Habu snake" venom on the renal glomerulus. *Keio J Med* 12:99–112, 1963
10. SUZUKI T: Experimentelle "Habu"-Gift-Nephritis. *Verh Jpn Pathol Ges* 7: 84–87, 1917
11. ISHIZAKI M: The presence of Thy-1.1 antigen in rat glomerular mesangial cells. *Allergy* 29:816–826, 1980
12. BAEHR G: Über experimentelle Glomerulonephritis. Ein Beitrag zur Lehre der Schrumphniere. *Beitr Pathol Anat* 55:545–574, 1913
13. SHEEHAN HL, DAVIS JC: Renal ischaemia with failed reflow. *J Pathol Bacteriol* 78:105–120, 1959
14. SHEEHAN HL, DAVIS JC: Renal ischaemia with good reflow. *J Pathol Bacteriol* 78:351–377, 1959
15. HERF S, POHL SL, STURGILL B, BOLTON WK: An evaluation of diabetic and pseudo-diabetic glomerulosclerosis. *Am J Med* 66: 1040–1045, 1979
16. KOBERNICK SD, WHITESIDE JH: Renal glomeruli in multiple myeloma. *Lab Invest* 6:478–485, 1957
17. OLSEN S: Mesangial thickening and nodular glomerular sclerosis in diabetes mellitus and other diseases. *Acta Pathol Microbiol Scand Section* A. 80(suppl 233):203–216, 1972
18. HILL GS, MOREL-MAROGER L, MERY JP, BROUET JC, MIGNON F: Renal lesions in multiple myeloma: their relationship to associated protein abnormalities. *Am J Kid Dis* 2:423–438, 1983
19. MANDALENAKIS N, MENDOZA N, PIRANI CL, POLLAC VE: Lobular glomerulonephritis and membranoproliferative glomerulonephritis. *Medicine* 50:319–355, 1971
20. HEPTINSTALL RH, JOEKES AM: Renal amyloid. A report on eleven cases proven by renal biopsy. *Ann Rheum Dis* 19:126–134, 1960
21. TEILUM G, LINDAHL A: Frequency and significance of amyloid changes in rheumatoid arthritis. *Acta Med Scand* 149:449–455, 1954
22. ACKER KJ VAN, BRANDE J VAN DEN, VINKE H: Membranous-proliferative glomerulonephritis. *Helv Pediatr Acta* 2:204–218, 1970
23. UEHLINGER VON E: Über die Schwefelkohlenstoff-Glomerulosklerose. *Schw Z Allg Pathol* 15:217–224, 1952
24. WELLMANN KF, VOLF BW: Renal changes in experimental hypercholesterolemia in normal and in subdiabetic rabbits. I. Short term studies. *Lab Invest* 22:36–49, 1970
25. WELLMANN KF, VOLK BW: Renal changes in experimental hypercholesterolemia in normal and subdiabetic rabbits. II. Long term studies. *Lab Invest* 24:144–155, 1971