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Granulomatous glomerulonephritis in Wegener's granulomatosis

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Summary. Review of the kidneys in 24 autopsy cases of Wegener's granulomatosis revealed a significant granulomatous glomerular lesion in eight of the cases. To gain a better understanding of this peculiar lesion, focusing on its pathogenesis, we attempted a thorough investigation on both glomerular and vascular lesions of the kidneys. Semiquantitative analysis of the glomerular lesions indicated that existence of a severe glomerular damage probably constitutes a necessary condition in the development of granulomatous glomerulonephritis, because the granulomatous glomerular lesion was typically seen in company with a widely distributed glomerular lesion represented by thrombotic and necrotic occlusion of capillary tufts and crescent formation. Necrotizing vasculitis in the kidney was always encountered, especially in small branches of renal arteries and vasa recta.

A serial section study of the two most typical cases indicated that granulomatous inflammation apparently originated in hilar arteriolitis, which extended along the pericapsular space and developed into diffusely circumferential periglomerular inflammation. We conclude that two factors are jointly at work, one inside and the other outside of the glomerulus in the pathogenesis of granulomatous glomerulonephritis: there is a thrombotic and necrotic lesion of the glomerular tuft, on the one hand and pericapsulitis originating in hilar arteriolitis on the other.

Key words: Wegener's granulomatosis – Granulomatous glomerulonephritis – Necrotizing angiitis.

Granuloma formation of a peculiar kind focusing on the glomeruli has been known most commonly as granulomatous glomerulonephritis. It has been observed in cases of Wegener's granulomatosis (Wegener 1936 and

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1939; Fienberg 1953; Godman and Churg 1954; Walton 1958; Howell and Epstein 1976) and of periarteritis nodosa (Davson et al. 1948; Ralston and Kvale 1949; McManus and Hornsby 1951; Buchanan et al. 1976). The granuloma is characterized both by a structure converging toward the center of the glomerulus and by the presence of epithelioid cells and giant cells with concomitant disruption of the glomerular and periglomerular structures. Despite the peculiar nature of the lesion, little discussion has been offered with regard to its prevalence, pathogenesis and clinicopathological significance.

Recently we had an opportunity to study 24 autopsy cases of Wegener's granulomatosis where we found variable degrees of granulomatous glomerular lesion in more than a half of the cases. In order to elucidate the factors contributing to the occurrence of this peculiar lesion, we carried out a detailed histological evaluation of both glomerular and vascular lesions in the kidneys of Wegener's granulomatosis combined with a serial section study in some selected cases. The results thus obtained indicated the likelihood that lesions located both inside and outside of the glomerulus jointly participated in the evolution of granulomatous glomerulonephritis.

Materials and methods

Twenty-four cases of Wegener's granulomatosis, subjects of autopsy between 1965 and 1981, were used as material for the present study. All 24 cases satisfied the morphological criteria for Wegener's granulomatosis proposed by Godman and Churg (1954). Morphological and clinical details in all but one case have been described elsewhere (Watanabe et al. 1981 and 1983). The patients, 11 of whom were male and 13 female, ranged in age from 15 to 64 years at the onset, which gave the average of 39.5 years. The duration of the disease was short in 13 cases, from two weeks to 12 months, while five patients lived more than three years including one that survived 14 years after the onset of the disease. In clinical terms, 22 patients showed evidence of renal damage such as proteinuria and haematuria; 10 of them died in uraemia.

All the paraffin-embedded blocks that were available were recut and stained with haematoxylin-eosin. Special stains employed as the need arose included periodic acid-Schiff, periodic acid-methenamine silver, Masson's trichrome, van Gieson's elastic stain, and phosphotungustic acid haematoxylin for fibrin. In addition, using 300 serial sections, we attempted three-dimensional observation of the granulomatous lesion in two cases with granulomatous glomerulonephritis (Cases 1 and 2) paying special attention not only to the extent of granulomatous inflammation but also to the changes in the hilar arterioles. Two cases without granulomatous glomerulonephritis (Cases 16 and 18) were also examined by serial sections in search of the hilar arteriolar lesion. Besides the granulomatous glomerular change, the extent of overall glomerular lesions was roughly analyzed in a random sample of 300 glomeruli by counting the number of those that exhibited thrombotic-necrotizing change, crescent formation, endocapillary proliferation, and sclerosing or fibrosing change. The final assessment assigned to each glomerulus was expressed in terms of a representative combination of these variables. At the same time, acute necrotizing and healed lesions of the renal blood vessels were assigned a grade from – to 3+ on the basis of the extent of the lesion and the number of vessels affected.

Results

The general morphological features of the kidney in all but one case have been described previously (Watanabe et al. 1981 and 1983). Briefly, the

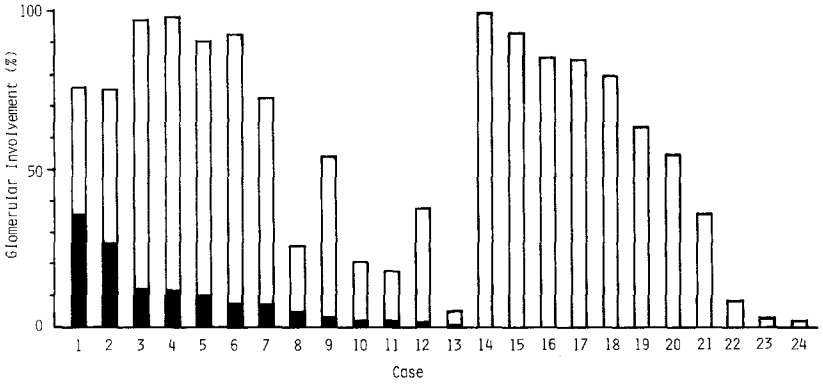

Fig. 1. Per cent distribution of glomerular involvement in 24 cases of Wegener's granulomatosis. Black columns represent granulomatous glomerular lesion, whereas white columns represent the other (non-granulomatous) ones

most characteristic change observed was a necrotizing, thrombotic and crescent forming glomerulonephritis in a focal and segmental distribution. The most remarkable change was the presence of areas of necrosis with destruction of one or more capillary loops associated with some polymorphonuclear cell exudation. The lesion could be attributed to an intracapillary thrombotic process leading to disintegration of the mesangium and rupture of capillary walls. In close proximity to this type of necrotizing change was proliferation of epithelial cells with formation of crescents. The healing stage was associated with fibrosis or sclerosis of the affected areas. Interpersed among these lesions were a number of glomeruli which showed the features of granulomatous glomerulonephritis. The distribution of the overall glomerular lesions was quite variable (Fig. 1) with a range from 2 to 99%: in 12 cases the affected glomeruli amounted to more than 70%, whereas there were five instances in which less than 20% of the glomeruli were involved.

Subclassification of the granulomatous glomerular lesion

Granulomatous glomerulonephritis is characterized by granulomata scattered in the cortex with involvement of both the glomeruli and the adjacent periglomerular tissue. The granulomatous infiltrate exhibited a radiating arrangement around the glomerulus which was becoming obsolescent. On the basis of its maturity and stage of development, each granulomatous lesion was further classified into one of the three types. In type 1, the lesion showed a severe inflammatory infiltrate accompanied by variable degrees of disruption of the glomerular and periglomerular structures (Fig. 2a). The radiating structure, if present, was not well defined, and few epithelioid cells and giant cells were observed. In type 2, the lesion was characterized by granulomatous foci in a radial arrangement around the obsolete or obsolescent glomerulus with participation of epithelioid cells, and frequently, giant cells were also present. Disruption of the glomerular architecture and the adjacent tissue was extensive, and therefore in a fully

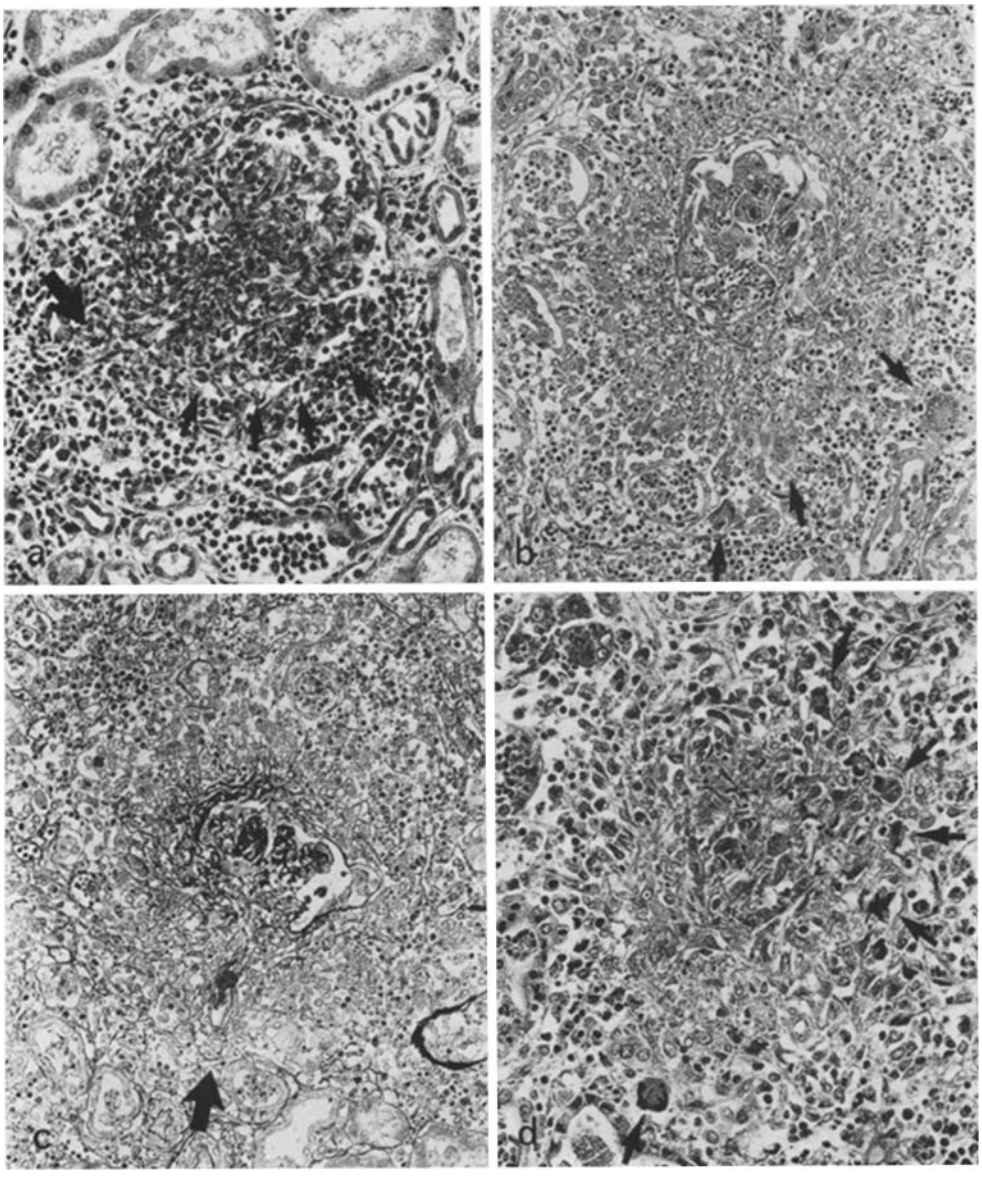

Fig. 2a–d. Some representative features of granulomatous glomerular lesions; type 1 **a** and type 2 **b, c,** and **d**. **a** Glomerulus and the surrounding tissue are infiltrated by inflammatory cells, associated with focal necrosis. Hilar arteriole (*thick arrow*) and Bowman's capsule (*thin arrows*) are blurred. Radial structure is inconspicuous (Case 2, HE, ×189). **b** Diffusely circumferential periglomerular granulomatous lesion. Radial arrangement of fibroblasts and histiocytes is well seen. Glomerular capillaries contain fibrin thrombi. *Arrows* indicate giant cells (Case 1, HE, ×143). **c** Similar mantle-like periglomerular lesion forming around a severely damaged glomerulus. Note fibrinoid necrosis and proliferative change of hilar arteriole (*arrow*) (Case 2, PAM-HE, ×143). **d** Fully developed lesion showing tubercle-like granuloma containing necrotic area in its center. Giant cells are indicated by *arrows* (Case 1, HE, ×229)

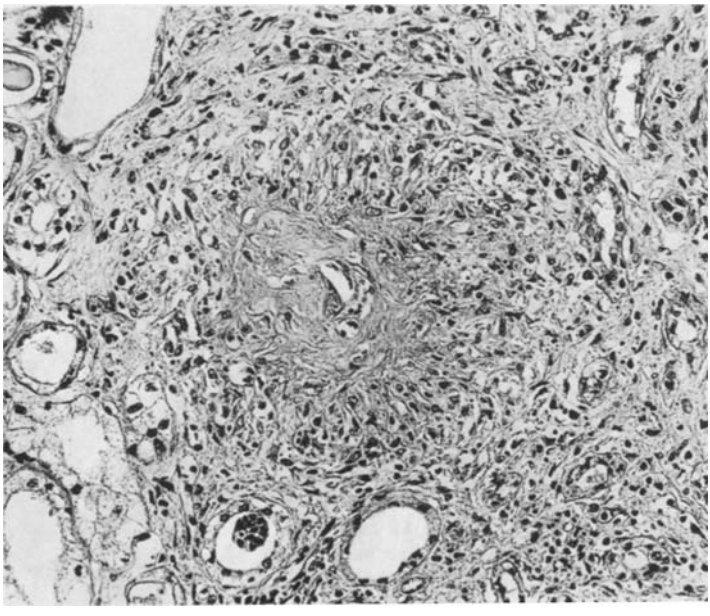

Fig. 3. Type 3 lesion showing radially arranged fibrosing components around an obsolete, totally sclerosed glomerulus. The lesion lacks a clear border and merges into the background tissue. (Case 6, HE, ×226)

developed lesion, remnants of the glomerulus were barely observable (Fig. 2b–d). In type 3, the lesion was a fibrosing or sclerosing phase of the granulomata centering on a glomerulus (Fig. 3).

Incidence of granulomatous glomerulonephritis. The granulomatous glomerular lesion was observed in 13 out of 24 cases. Its incidence in 300 glomeruli ranged from 0.7 to 35.3% (Fig. 1). To clarify the pathogenesis of this peculiar lesion, we focused on the eight cases with more than 5% of the glomeruli involved, taking these as cases with granulomatous glomerulonephritis. As is summarized in Table 1, the group consisted of five men and three women, six of them middle-aged or older. Most of them took a rapid course, and six died within seven months after the onset of the desease. In six cases symptoms and signs of renal failure were predominant in the terminal clinical picture. In addition to the granulomata of the respiratory tract, necrotizing vascular lesions were widespread in many organs.

Glomerular lesions in cases with granulomatous glomerulonephritis. A semiquantitative analysis of glomerular lesions revealed a high degree of glomerular involvement, ranging from 73 to 97%, in all but one cases with granulomatous glomerulonephritis (Table 2). Furthermore, in five cases with types 1 and 2 lesions, acute changes that could be considered as thrombotic-necrotizing were predominant, whereas in Cases 4, 5, and 6, in which only type 3 lesion was observed, more than 75% of the glomeruli were sclerotic. It was suspected, therefore, that destruction of the tuft structure due to

Table 1. Cases with granulomatous glomerulonephritis

Case	Age at onset (years), sex	Clinical duration	Respiratory tract lesion	Sites of angiitis
1.	41, F	2 weeks	lung, larynx	heart, kidney, spleen, ovary, lymph node, bone marrow
2.	46, F	15 months	nose, lung	heart, kidney, liver, thyroid, ovary
3.	64, F	7 months	lung	heart, kidney, liver, oesophagus, ovary, uterus
4.	19, M	5 months	nose, lung	kidney, spleen, intestine
5.	36, M	34 months	nose, lung, larynx	kidney, spleen, pancreas, aorta
6.	55, M	7 months	nose, lung, pharynx, larynx	kidney, stomach, pancreas, skin, prostate, testis
7.	62, M	3 months	lung, pharynx	kidney, liver, intestine prostate
8.	43, M	7 months	nose, lung, pharynx	heart, kidney, adrenal, testis, prostate

Table 2. Distribution of glomerular and vascular lesions in cases with granulomatous glomerulonephritis

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Glomerular lesions[a]								
Granulomatous glomerular lesions								
Type 1	8.3	10.3	4.7	0	0	0	5.7	3.0
Type 2	27.0	15.3	6.0	0	0	0	1.0	2.0
Type 3	0	0	1.3	11.3	9.7	7.3	0	0
Other glomerular lesions								
Thrombotic-necrotizing	22.7	19.3	14.3	1.3	0	1.7	40.7	9.3
Thrombotic-necrotizing and crescentic	7.7	18.0	30.3	2.7	0	1.3	14.7	4.7
Proliferative crescentic	9.3	10.7	17.7	0.3	0	7.0	9.0	4.7
Sclerosing or fibrosing	2.0	1.3	22.7	81.7	80.3	75.3	1.7	1.7
Total	77.0	75.0	97.0	97.3	90.0	92.7	72.7	25.3
Vascular lesions								
Interlobar and arcuate a.	1+	1+	1+	–	2+	2+	1+	–
Interlobular a. and arterioles	3+	2+	3+	2+	2+	1+	2+	1+
Vasa recta and venules	3+	3+	3+	–	–	2+	2+	–

[a] Each number shows the percentage of the individual lesion in randomly chosen 300 glomeruli

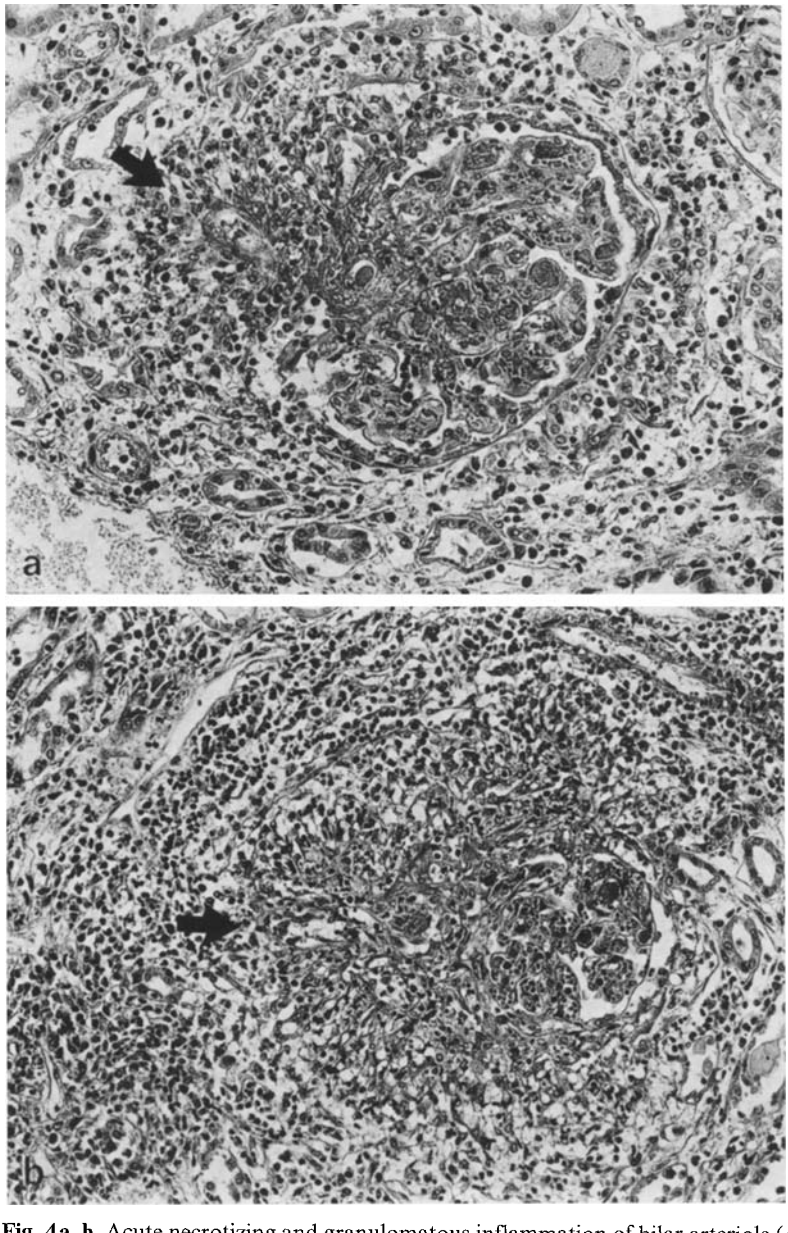

Fig. 4a, b. Acute necrotizing and granulomatous inflammation of hilar arteriole (*arrows*), seemingly extending along the pericapsular space. **a** Granulomatous inflammation mainly located around a hilar arteriole (Case 2, HE, ×226). **b** Fan-shaped expansion of granulomatous inflammation more widely enveloping the glomerular structure. (Case 1, HE, ×176)

Table 3. Extent of periglomerular inflammation and incidence of apparent hilar arteriolitis using serial sections in Cases 1 and 2

	Periglomerular inflammation				Hilar arteriolitis
	Diffusely circumferential	Predominantly in		Undefinable	
		Vascular pole	Urinary pole		
Case 1	50	44	2	4	64
Case 2	44	51	3	2	71

Each number shows incidence in 100 glomeruli with granulomatous lesion

thrombotic-necrotizing lesion might provide a predisposing condition for granulomatous glomerular lesion.

Vascular lesions. Vasculitis in the kidney was invariably noted in all cases with granulomatous glomerulonephritis (Table 2). The main blood vessels involved were interlobular arteries, arterioles, and venules or vasa recta, although larger vessels, such as those of the arcuate size or even larger, occasionally showed inflammatory necrotizing changes. Noteworthy was the fact that in Cases 1, 2, and 3, where types 1 and 2 granulomatous lesions were observed a great deal, vasculitis of smaller vessels such as interlobular arteries, arterioles, and vasa recta appeared to be predominant. However, in cases without the granulomatous glomerular lesion, vasculitis of the kidney was infrequent; it was sporadically observed in only three cases.

Serial section study. Results of the serial section study conducted in Cases 1 and 2 are given in Table 3. Although in each glomerulus the extent and the three-dimensional distribution of periglomerular inflammation were variable, the results could be roughly summarized as follows. In a fully developed lesion, granulomatous inflammation typically extended itself diffusely and totally encompassed severely damaged glomerular structures (Fig. 2b–d). When the inflammation was rather localized, it was preferentially located at the vascular pole (Fig. 4).

The wall of the hilar arterioles frequently disclosed disorganization with replacement by numerous inflammatory cells often accompanied by fibrinoid necrosis. In Cases 1 and 2, we observed such an arteriolar involvement in at least 64 and 71, respectively, of 100 granulomatous lesions (Table 3). Most of the remaining glomeruli showed advanced lesions with the arteriolar structure no longer visible because of severe inflammation. The cellular reaction spread to the tissue surrounding the arterioles and further along the pericapsular space, often giving rise to a fan-shaped lesion around the glomerular structures (Fig. 4b).

In contrast, the serial section study in Cases 16 and 18, both with wide-

Table 4. Per cent distribution of granulomatous glomerular lesion in three zones of the cortex

	Zone of cortex			Whole cortex
	Outer 1/3	Middle 1/3	Inner 1/3	
Case 1	50	32	24	35.3
Case 2	39	19	19	25.7
Case 3	17	11	8	12.0
Case 4	15	16	3	11.3
Case 5	9	10	10	9.7
Case 6	12	5	5	7.3
Case 7	5	7	9	6.7
Case 8	3	5	7	5.0

spread glomerular lesion of more than 80% but with no granulomatous glomerular lesion, failed to reveal arteriolitis of the vascular pole.

Distribution of granulomatous glomerular lesions. Distribution of the lesion in the renal cortex was roughly expressed in terms of the percentage of glomeruli with granulomatous lesion in the three zones of the cortex. As is seen in Table 4, granulomatous glomerular lesion was more prevalent in the outer layer of the cortex in Cases 1 to 4 and in Case 6.

Discussion

The first description of granulomatous glomerulonephritis was given by Wegener (1936) under the name of "periglomeruläres Granulom", when he referred to the condition as a previously undescribed lesion. Wegener was precise enough in his description of the granuloma, pointing out that it had a radiating structure centering on a glomerulus; he also emphasized a serious nature of the lesion, i.e., that it evolves to complete destruction of the glomerular structures. In 1939, he proposed the term "granulomatöse Glomerulonephritis" in view of such granulomata being a prominent feature in the kidney (Wegener 1939). About ten years later, Davson et al. (1948) observed a similar lesion in three of 14 cases of periarteritis nodosa. Granulomatous glomerulonephritis was also reported in a patient with systemic vasculitis associated with polyarthritis (McManus and Hornsby 1951).

The precise incidence of the lesion has remained obscure despite some other reports of its occurrence in cases with Wegener's granulomatosis (Fienberg 1953; Godman and Churg 1954; Walton 1958; Howell and Epstein 1976) and periarteritis nodosa (Ralston and Kvale 1949; Buchanan et al. 1976). Heptinstall (1983) goes only so far as say that the lesion was not necessarily observed in all cases of Wegener's granulomatosis. Nor has there been much discussion as to the morphogenesis of the lesion. The suggestion made in McManus and Hornsby (1951) that the afferent arteriole serves as a nidus of periglomerular inflammation we find rather lacking in substantive investigation.

Analysis of the overall pattern of glomerular lesions in the present study

suggests a close relationship between granulomatous glomerular lesion and severe glomerular damage represented by thrombotic-necrotizing and crescentic processes, which have been regarded as basic glomerular alterations in Wegener's granulomatosis (Godman and Churg 1954; Watanabe et al. 1981). It is conceivable, therefore, that the existence of severely damaged glomeruli constitutes a necessary condition for the evolution of granulomatous glomerulonephritis.

Evidence accumulated in both human (Morita et al. 1973; Min et al. 1974) and experimental glomerulonephritis (Vassalli and McCluskey 1964; Watanabe and Tanaka 1976) indicates that the development of extracapillary lesion is probably due to severe injury to the capillary loops such as necrosis and basement membrane damage together with leakage of fibrin-fibrinogen into the capsular space. In cases where the extracapillary reaction is severe, infiltrates of inflammatory cells may be observed around Bowman's capsule. In common glomerulonephritis, however, pericapsular inflammation is inconspicuous and seldom develops the granulomatous type of reaction.

Another factor that demands consideration is the vascular lesion, since granulomatous glomerulonephritis is invariably accompanied by necrotizing vasculitis, which particularly affects smaller vessels. Additionally, we have occasionally observed marked arteriolar involvement in the midst of the inflammatory focus at the vascular pole even in ordinary histological sections. But is was not until we performed a serial section study that the hilar arteriolar lesion was evidently involved at a high frequency – high enough a frequency to suggest a causal relation to the granuloma formation. The results of the study indicate that the granulomatous inflammation apparently originates in the vascular pole manifesting itself as hilar arteriolitis.

On the basis of the foregoing, we would suggest that two factors are jointly at work in the evolution of granulomatous glomerulonephritis: the first is a thrombotic-necrotizing lesion of the capillary tuft, and the second pericapsulitis derived from hilar arteriolitis. The presumed process of morphogenesis of the granulomatous glomerular lesion is shown in Fig. 5. Thrombotic-necrotizing change of capillary tufts, often accompanied by extracapillary reaction, is a necessary condition. Granulomatous inflammation invariably occurs in the vascular pole manifest by hilar arteriolitis. The inflammation then spreads along the pericapsular space forming a converging structure toward the glomerulus in which necrosis and destruction of tuft structures are more advanced. Finally these inflammatory processes result in the formation of a fully developed granuloma radiating around the remnants of a glomerulus.

Finally, the term granulomatous glomerulonephritis may be slightly misleading, for it gives the impression that it is an independent disease entity. On the other hand, "granulomatous glomerulitis" or "granulomatous periglomerulitis" does not seem appropriate either, as neither sufficiently express the extension and genesis of the lesion. The fundamental glomerular lesion in Wegener's granulomatosis is thrombotic and necrotizing change in a focal and segmental distribution (Godman and Churg 1954; Watanabe

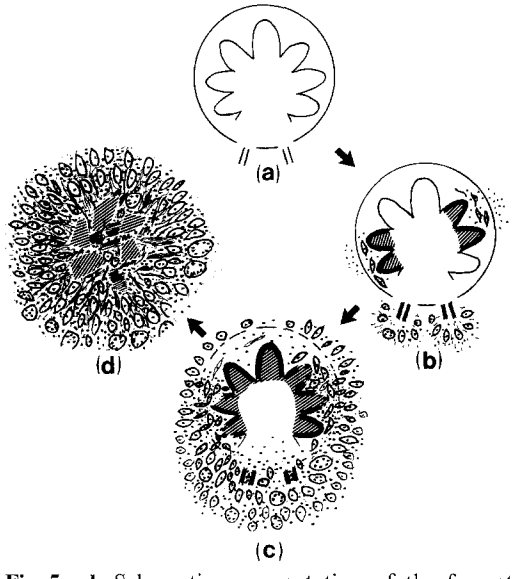

Fig. 5a–d. Schematic representation of the formation of granulomatous glomerular lesion. **a** Normal glomerulus, Bowman's capsule, and hilar arterioles. **b** Granulomatous inflammation occurs in hilar arterioles. Glomerular tuft shows thrombotic and necrotic change. Extracapillary proliferation becomes apparent, variably associated with banal pericapsulitis. **c** Thrombotic and necrotic change of the glomerular tuft is more advanced. Circumferential granulomatous inflammation is formed around the capsule, but the main focus is still present in the vascular pole. **d** Fully developed granulomatous lesion is made up of epithelioid cells and giant cells radially arranged around the remnants of a glomerulus

et al. 1981). Although there are cases where the granulomatous glomerular lesion is absent, approximately one-third of the cases with Wegener's granulomatosis in the present study disclosed significant degrees of this peculiar lesion. In addition, it is noteworthy that its evolution has a close relationship with necrotizing inflammation of the hilar arterioles. It seems appropriate, therefore, to apply the term granulomatous glomerulonephritis at least in cases where this peculiar lesion is a prominent feature of the kidney.

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