Participation of intravascular coagulation in the pathogenesis of glomerular and vascular lesions

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Evidence of both generalized and localized intravascular coagulation can be found in a wide variety of diseases which cause lesions of glomeruli, arteries and arterioles in the kidney.

In conditions in which fibrin is deposited in vessels or glomeruli, the clinical course and morphological evolution of the lesions vary widely. In the most benign type of glomerular lesion, namely that of acute tubular necrosis, in spite of well-documented evidence of coagulation within glomeruli [1—3], lesions are mild and appear to be fully reversible. At the other end of the scale, where abundant fibrin is present as in the thrombotic microangiopathies, scleroderma and malignant hypertension, total occlusion of vessels and glomeruli progresses rapidly in untreated patients and a uremic death is common. Pre-eclamptic toxemia occupies an intermediate position. The similarities and differences within this group of diseases are discussed and illustrated.

Methods

The biopsy specimens illustrated are part of a series of 4,860 renal biopsies carried out over a 15-yr period at this hospital. Twenty-four serial sections cut at 1 to 2 μ are stained with hematoxylin-eosin, periodic acid-Schiff, Masson's and picromallory trichrome stains, silver methenamine, Weigert's elastic and von Gieson's methods.

Since 1965 selected biopsy specimens have been studied by electron microscopy and since 1970 the presence of immunoglobulins (IgG, IgA, IgM) complement and fibrin has been sought using fluorescein-labelled antisera.

For electron microscopy, material is fixed in 1% glutaraldehyde buffered to pH 7.2 with cacodylate and postfixed with osmium tetroxide. One-mm diced tissue segments are embedded in Araldite/Durcupan mixture and cured to maximum hardness in 72 hr. Sections are cut at 300 to 500 Å and examined with an electron microscope (Hitachi) at an accelerating voltage of 75 kv.

For fluorescent microscopy tissue is snap-frozen at the time of biopsy and sectioned in a cryostat at −20°C. Sections are stained by the direct method using commercial fluorescein-labelled antisera against IgA, IgG, IgM, C3, fibrinogen and albumin.

Results

Table 1 lists the groups of diseases in which there is evidence of thrombosis or fibrin deposition within glomeruli and vessels in the kidney.

Lesions in which fibrin is present, usually without associated immunoglobulins. 1) Acute tubular necrosis. Several studies [1—3] demonstrate conclusively that local intravascular coagulation occurs in the kidney in acute tubular necrosis. While deposition of fibrin in the glomeruli may contribute to the oliguria in this condition, there is a discrepancy between the amount of fibrin which can be demonstrated in glomeruli [2] and the degree and duration of renal failure. The relatively small amounts of fibrin could not, by obstructing glomerular capillaries, account for the prolonged period of oliguria. Cessation of renal blood flow can be observed in renal tissue within minutes of injection of glycerol in experimental acute tubular necrosis [4] (Fig. 1). Fibrin may form in renal vessels and glomeruli within the areas of stasis which can be demonstrated experimentally. Irregular constrictions in the renal vessels [4] and the turbulent flow which results could also lead to platelet aggregation, endothelial damage and fibrin deposition. It seems likely that the cessation
of blood flow in the cortical blood vessels is the major factor accounting for the renal failure [4]. Variable flow returns over a period of days following an injection of glycerol [4]. Swelling of glomerular endothelial cells visible on electron microscopy may accompany fibrin deposition in the acute stage but, subsequently, complete and rapid resolution of glomerular lesions usually occurs. Interlobular arteries and afferent arterioles show irregular areas of constriction during

the period when flow in arteries, arterioles and glomeruli ceases, but the degree of constriction is not sufficient to account for the alteration in blood flow. Using the model illustrated in Fig. 1, far more intense vasoconstriction occurs following an injection of angiotensin before blood flow ceases [5]. Blood flow continues in ear chamber vessels around the kidney grafts when flow in the renal grafts has ceased in the model illustrated in Fig. 1 [4].

2) Pre-eclamptic toxemia. a) Glomerular lesions. In acute tubular necrosis there is probably a relatively short period of fibrin deposition in renal glomeruli over a period of days related to primary cessation of renal blood flow and vasoconstriction. In contrast, in pre-eclamptic toxemia large deposits of granular fibrinoid material (Fig. 2), which give a positive result with specific antifibrinogen-labelled antisera, are probably deposited over a much longer period of time as a manifestation of chronic low-grade intravascular coagulation [6]. These deposits only occasionally contain identifiable fibrin fibrils (Fig. 2).

In spite of the fact that lesions are usually partly, or completely, reversible over a period of months following pre-eclamptic toxemia, there may be very marked abnormalities in the acute stage. The lesions in glomeruli are far more pronounced (Fig. 2) and cause much more obstruction to blood flow than those illustrated in acute tubular necrosis [1, 2], and yet these well marked glomerular lesions are usually

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**Table 1. Glomerular and vascular lesions in the kidney in which fibrin can be demonstrated**

<table>
<thead>
<tr>
<th>Lesion in which fibrin is present usually without associated immunoglobulins</th>
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<td>A. Reversible lesions</td>
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<td>1. Acute tubular necrosis</td>
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<td>2. Pre-eclamptic toxemia</td>
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<td>B. Progressive and persistent lesions</td>
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<td>1. Thrombotic microangiopathies (including postpartum renal failure)</td>
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<td>2. Scleroderma</td>
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<td>3. Malignant hypertension</td>
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<th>Lesion in which fibrin and immunoglobulins are present</th>
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<td>A. Allograft rejection</td>
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<td>B. Glomerulonephritis</td>
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<td>C. Systemic diseases such as lupus erythematosus and Goodpasture's syndrome</td>
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**Fig. 1.** a, Three functioning transplants of fetal kidney tissue in a transparent rabbit ear chamber prior to injection of glycerol. The hemorrhagic area on the top left-hand side is a nonfunctioning hemorrhagic failed transplant. b, The same three kidney grafts following injection of glycerol. Blood flow has ceased in the kidney tissue but is continuing in the ear chamber vessels at the periphery of the field.
accompanied by only mild impairment of renal function in pre-eclamptic toxemia. The reduplication of basement membrane which develops in association with the subendothelial deposits may be well marked and closely mimic the double contours seen in mesangiocapillary glomerulonephritis (Fig. 3). The mesangiocapillary glomerular changes may persist for months after pregnancy and may continue to improve in serial biopsy specimens for as long as 18 months after the acute episode of pre-eclamptic toxemia [7].

While pre-eclamptic toxemia is usually regarded as a condition in which only fibrin and no immunoglobulins are deposited in glomeruli, immunoglobulins may be present in the acute stage. The lesions illustrated in Fig. 2 were associated with IgA, IgG, IgM and complement as well as fibrin but showed complete resolution on light microscopy and electron microscopy in a period of three months. Similar findings have been reported in a series of cases of pre-eclamptic toxemia [8].

In pregnancy toxemia during resolution of lesions, collagen fibrils have not been observed within the basement membrane in contradistinction to the more serious groups of disorders discussed in the following in which fibrin deposition in the acute stage is followed by collagen formation during "healing" [9]. Collagen formation in experimental animals may appear within days of the injury.

b) Arteriolar and arterial lesions. Arteriolar and arterial lesions accompany glomerular lesions of pre-eclamptic toxemia in the acute stage (Fig. 4). While hypertension is usually present, the blood pressure may be only slightly elevated during an episode of pre-eclamptic toxemia and the changes in blood vessels often appear more severe than one would expect for the level of blood pressure recorded. The arteriolar lesions are so similar in appearance and staining reaction to those within glomerular capillaries (Fig. 4) that it seems likely that the same process which causes subendothelial deposition of fibrinoid material in glomerular capillaries is responsible for the fibrinoid subendothelial deposits in arterioles. Lesions in arterioles and arteries may persist for years in patients who have had pre-eclamptic toxemia, although improvement may be seen in serial biopsy specimens in some patients. Changes of cellular intimal proliferation in interlobular and arcuate arteries (Fig. 5) are often more prominent than arteriolar lesions in specimens from biopsies which are carried out months or years after an episode of pre-eclamptic toxemia. They may
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Fig. 3. Glomerulus from a patient with severe pre-eclamptic toxemia showing the double contour or mesangiocapillary change with reduplication of the basement membrane in several capillaries (silver methenamine, P.A.S., x 900). Large fibrinoid deposits lie between the original basement membrane and the newly formed argyrophitic layer of basement membrane.

be well marked in normotensive patients following an episode of pre-eclamptic toxemia (Fig. 5).

Although vessel lesions may improve following an episode of pre-eclamptic toxemia, there may be an increase in the lesions with successive pregnancies [7]. In an occasional patient without glomerular disease, in whom a biopsy specimen is available prior to pregnancy, arterial and arteriolar lesions have been seen to increase during the first pregnancy [7]. When vessel lesions such as those in Figs. 4 and 5 are present following an episode of pre-eclamptic toxemia, even if the blood pressure is normal at the time of the biopsy, toxemia almost always recurs in subsequent pregnancies.

2) Thrombotic microangiopathies. Such conditions as the hemolytic-uremic syndrome which classically occurs in children, postpartum renal failure and other conditions with similar clinical manifestations of intravascular coagulation and morphological findings in the kidney are included.

a) Glomerular lesions. The glomerular lesions in the acute stage of the hemolytic-uremic syndrome were well described by Habib et al [10]. The reduplication of the basement membrane in glomerular capillaries (Fig. 6) is very similar to that illustrated in Fig. 3 in pre-eclamptic toxemia. On electron microscopy, in contrast to the dense granular subendothelial deposits of fibrinoid material usually seen in pre-eclamptic toxemia (Fig. 2), the subendothelial zone is translucent in the hemolytic uremic syndrome [9–11]. This translucent zone may contain identifiable fibrin fibrils [9]. In spite of the translucent or “empty” appearance of the subendothelial zone and relative rarity of identifiable fibrin fibrils on electron microscopy, abundant fibrin is seen in glomeruli when specific fluorescein-labelled antifibrin sera are used [12].

Patients with thrombotic microangiopathies such as the hemolytic-uremic syndrome frequently die of uremia in the acute stage. If they recover, however, unlike patients with acute tubular necrosis or pre-eclamptic toxemia, they show double contours and collagen fibrils within the basement membrane (Fig. 7) [9, 11]. This is a feature of the group of lesions with a poor prognosis in which fibrin deposition in glomeruli is a prominent feature in the acute state [9, 11]. Spontaneous recovery is rare in such patients; however, they may recover following heparin administration [11, 13–15].

The major difference between thrombotic microangiopathies in children and adults seems to be in the greater prominence of arterial and arteriolar changes in adults [16]. Glomeruli which lie distal to severely narrowed arteries and arterioles may show marked wrinkling of the glomerular capillary walls (Fig. 6). In the same biopsy specimen, a glomerulus which is supplied by a patent afferent arteriole and interlobular artery may show the “double contour” appearance without wrinkling, and an adjacent glomerulus distal to a narrowed or occluded arteriole may show marked wrinkling of the basement membrane characteristic of ischemia. Occasionally, within one glomerulus the characteristic “double contour” of the glomerular capillary wall may be present in patent glomerular capillaries, and marked wrinkling of the basement membrane is seen in collapsed capillaries in which blood flow has ceased, presumably due to thrombosis in glomerular capillaries (Fig. 6).

b) Arterioles and arteries. Children with the hemolytic uremic syndrome show a varying degree of occlusion and narrowing of arteries and arterioles by fibrin or by cellular intimal proliferation (Fig. 8, a–d). In adults, lesions in arteries and arterioles are usually very prominent, particularly when thrombotic microangio-
Atheries develop in the postpartum period [7]. The vessel lesions are similar in appearance but more extreme in degree than those in pre-eclamptic toxemia [7, 11]. They also closely resemble lesions in scleroderma, malignant hypertension and allograft rejection, and the similarity of these lesions and participation of coagulation and fibrin deposition in their pathogenesis is evident from the stages in their evolution (Fig. 8, a–d). An acute thrombotic microangiopathy provides one of the best opportunities of studying the stages in development of the lesions in arteries. Different arteries in the same biopsy specimen (Fig. 8, a–d) show the different stages in the "organization" of extensive fibrin deposits in interlobular arteries. This process of organization leads to considerable narrowing of many arteries. Leakage of fibrin into the media of the arteries may accompany fibrin deposition within the lumen (Fig. 8, b and c) as in malignant hypertension [19].

Although the vessel lesions closely resemble those of malignant hypertension, patients usually have a normal blood pressure early in the course of the disease but may develop fulminating malignant hypertension as a terminal event. Severe narrowing of interlobular arteries may precede and presumably cause hypertension in such patients.

3) Scleroderma. The renal lesions which develop in scleroderma predominantly affect arteries and arterioles and can be almost identical with those seen in the thrombotic microangiopathies.

In patients with acute scleroderma, lesions involving...
renal arteries and glomeruli are usually accompanied by a fulminating course and progression to renal failure. The clinical course often closely mimics that of the thrombotic microangiopathies.

Fibrin deposition can be clearly demonstrated in renal glomeruli [11] and vessels (Fig. 9) and immunoglobulins are usually absent.

a) Glomerular lesions. Glomeruli in scleroderma may show reduplication of the basement membrane similar to that illustrated in pre-eclamptic toxemia and the hemolytic-uremic syndrome [9, 11]. As in thrombotic microangiopathies, the degree of wrinkling of the glomerular capillary walls is related to the degree of obstruction to blood flow in the related afferent arteriole and interlobular artery. In the acute stage translucent subendothelial areas are seen and in the “healing” phase collagen is present in a subendothelial position in the glomerular capillary [9, 11]. This is a common feature in other diseases in which fibrin deposition is prominent in the acute stage and in which the prognosis is poor [9, 11].
b) Arterial and arteriolar lesions. The arterial lesions in scleroderma are more prominent than glomerular lesions, and arterial lesions correlate better with the degree of renal failure than the glomerular lesions. Most interlobular arteries are almost totally occluded by cellular intimal proliferation (Fig. 9) very similar to that which develops during "organization" of fibrin in thrombotic microangiopathies (Fig. 8, a–d). In both conditions different stages in the process of organization can be seen in the same biopsy specimens. Fibrin may be obvious within this cellular intimal layer on light microscopy (Fig. 9). Even when fibrin is not obvious on light microscopy, it can be detected by fluorescent and electron microscopy. As in the case of thrombotic microangiopathies, in spite of the close resemblance between the arterial changes in scleroderma and those of malignant hypertension, patients with scleroderma may be normotensive initially, and fulminating malignant hypertension may develop after occlusive vessel lesions such as those in Fig. 9 have been demonstrated in a renal biopsy specimen [11]. The kidney of a patient with scleroderma who has run this fulminating course differs from the kidney in a patient with essential malignant hypertension in that it shows multiple, small cortical infarcts [20]. This frank infarction of small areas of cortex supplied by totally occluded in-
terlobular arteries presumably reflects the rapidity with which the vessels are occluded. The rapidity of development of lesions in scleroderma is also suggested by the more prominent fibrin deposits within the intimal layer on light microscopy (Fig. 9). Such frank deposits of fibrin are only rarely encountered in malignant hypertension [20] and have been particularly prominent in patients with postpartum renal failure and malignant hypertension [20]. In retrospect, these patients almost certainly had primary postpartum thrombotic microangiopathy and secondary malignant hypertension. In scleroderma as in thrombotic microangiopathies, the cellular proliferation which occludes interlobular arteries is likely to result from "organization" of fibrin deposited in arteries and arterioles (Fig. 9).

4) Malignant hypertension. There is now abundant evidence that intravascular coagulation is a prominent feature in the malignant phase of hypertension [21–23].

a) Glomerular lesions. Apart from capillary loop thrombi in glomeruli in malignant nephrosclerosis (Fig. 10), [20] the major change on light microscopy is the wrinkling of the walls of glomerular capillaries related to ischemia induced by severe narrowing of arteries and arterioles [11]. On electron microscopy, however, a translucent subendothelial zone is seen (Fig. 11). This may contain scattered fibrin fibrils [26]. This
change closely resembles the classical translucent subendothelial zone seen in the thrombotic microangiopathies [10].

We have demonstrated that the translucent subendothelial zone in malignant hypertension and in the thrombotic microangiopathies is associated with diffuse positive fibrin staining when fluorescein-labelled antifibrin antisera are used.

b) Lesions in arteries and arterioles. The lesions in arteries in untreated malignant hypertension closely mimic those seen in normotensive patients with thrombotic microangiopathies or scleroderma (Fig. 12).

The steps in the morphological evolution of the lesions of malignant hypertension have created much controversy. The work of Giese [19] has illustrated the importance of endothelial damage and increased permeability of the vessel wall. This mechanism, while it explains so-called fibrinoid necrosis seen in arteriolar walls in malignant hypertension, cannot account for the narrowing by cellular intimal proliferation seen in interlobular arteries, which is the most characteristic feature of malignant hypertension [20]. Seepage of fibrin and other substances into the vessel wall in malignant hypertension closely resembles the appearance in Fig. 8. This change occurs in any acute vessel damage such as that seen in malignant hypertension, allograft rejection, arteritis and thrombotic microangiopathies. A far more important lesion in terms of deterioration of renal function is the cellular intimal proliferation which causes marked narrowing of interlobular arteries in all these conditions. This so-called onion layering in interlobular arteries correlates well with renal failure in malignant hypertension [20].

In the untreated patient, malignant hypertension runs the same fulminating course as scleroderma and the thrombotic microangiopathies, the majority of patients dying of renal failure in less than two months [20].

The marked similarities between interlobular artery lesions in malignant hypertension, scleroderma and the thrombotic microangiopathies are very suggestive that all three have a similar pathogenesis.

The vessel lesions of malignant hypertension cannot be attributed to the blood pressure alone. Age- and sex-matched patients with and without malignant hypertension have similar blood pressure readings [20]. Some other factor, possibly a sudden rise in vasoactive
agents such as angiotensin and noradrenalin, and the remarkable alteration in both the caliber and the endothelium of blood vessels produced by these agents, [5] (unpublished data) might be the primary factor which initiates the syndrome of malignant hypertension. Platelet thrombi form in such vessels both following angiotensin infusion [5] and very soon after ligation of the aorta in experimental malignant hypertension (unpublished data). Irregular areas of vasoconstriction together with platelet thrombi and the associated endothelial damage which they can cause may both initiate and perpetuate the so-called “vicious cycle” of malignant hypertension (unpublished data). In malignant hypertension, as in scleroderma and thrombotic microangiopathies, the rapid occlusion of interlobular arteries in the kidney could well result from “organization” of fibrin in these vessels. The lesions illustrated in Fig. 8, a–d strongly suggest that this is the mechanism whereby interlobular artery narrowing develops in these conditions.

5) Lesions in which fibrin and immunoglobulins are present. In the group of glomerular and vascular lesions in Table 1 in which deposits of immunoglobulins accompany fibrin deposition, it may be difficult to assess the relative role of coagulation and immunologic damage in the pathogenesis of lesions.

The lesions in glomeruli in allograft rejection [9, 11, 24, 25], glomerulonephritis [9, 11] and systemic diseases such as polyarteritis nodosa [9] may closely resemble those discussed and illustrated above in the thrombotic microangiopathies, scleroderma and malignant hypertension.

Glomerular lesions in allograft rejection may be identical with the mesangiocapillary change illustrated in Fig. 3 [9, 11, 25, 27]. Collagen formation within the glomerular basement membrane is particularly prominent in biopsy specimens of allograft rejection [9, 11, 25, 26]. It is also seen in the more serious glomerular lesions such as polyarteritis nodosa, Goodpasture’s syndrome and experimental glomerulonephritis induced by antiglomerular basement membrane antibody [9, 11]. In mesangiocapillary glomerulonephritis, the characteristic morphologic feature is that of reduplication of the basement membrane giving a “double contour” appearance such as that illustrated in Figs. 3, 6 and 11. Collagen within peripheral capillaries is rare in this form of glomerulonephritis.

Lesions in interlobular arteries in allograft rejection (Fig. 13) and polyarteritis nodosa closely resemble those discussed and illustrated in scleroderma and malignant hypertension and the thrombotic microangiopathies. In allograft rejection serial biopsy specimens show that fibrin deposition and “organization” by cellular intimal proliferation may progress very rapidly in a period of only a few days following transplantation [24, 25].
Discussion

The remarkable similarity between the lesions in interlobular arteries in the thrombotic microangiopathies, scleroderma and malignant hypertension (Figs. 8, 9 and 12) suggests that all have a similar pathogenesis. It is proposed that fibrin deposition within vessels (Fig. 8, a–d) is the first step in the formation of the intimal lesions which cause severe narrowing of interlobular arteries in all three conditions. Different stages including early fibrin deposition alone (Fig. 8a), fibrin with commencing organization and epithelialization (Fig. 8b) and narrowing by cellular intimal proliferation (Figs. 8d, 9 and 12) may all be present in the same biopsy specimen (Fig. 8, a–d). Serial sections of the same interlobular artery may show different stages in this process (Fig. 8, a–d). These observations are difficult to interpret unless “organization” of fibrin within interlobular arteries accounts for the narrowing by cellular intimal layers in conditions such as the thrombotic microangiopathies, scleroderma and malignant hypertension [24]. Lesions in allograft rejection probably develop in the same way [11, 24, 25].

The fact that such vessel lesions may precede the development of hypertension in the thrombotic microangiopathies and scleroderma raises the possibility that the characteristic lesions in interlobular arteries in malignant hypertension may be the cause and not the result of the elevated blood pressure. Direct in vivo observations of the vessels in a rat back chamber during the development of malignant hypertension show remarkable alterations in the caliber of vessels as a very early change and subsequent thrombus formation and intimal changes (unpublished data).

Although interlobular artery lesions such as those illustrated in Figs. 8 and 9 may precede hypertension, such patients usually later develop fulminating hypertension which may well be due to the ischemia produced by the lesions in interlobular arteries.

Glomerular lesions associated with fibrin deposition show a gradation in severity from acute tubular necrosis, where fibrin deposition leaves no residual glomerular abnormalities, to pre-eclamptic toxemia where subendothelial deposits become enclosed by reduplicated layers of basement membrane (Fig. 3), which may persist for months, to thrombotic microangiopathies and scleroderma in which the reduplicated layers of basement membrane seen in the acute stage (Fig. 6) are followed by collagen deposition in glomerular capillaries during healing (Fig. 7). In conditions such as allograft rejection, mesangiocapillary change is prominent and progressive and the clinical course in such patients may closely mimic that of mesangiocapillary glomerulonephritis [27]. Collagen formation is also
prominent in the glomerular basement membrane in chronic allograft rejection and polyarteritis nodosa.

Acknowledgments

Mr. D. C. Mathews carried out the electron microscopy, and Mr. Ian Birchall and Ms. Rosemary Berry prepared the other microscopic sections.

Reprint requests to Dr. Priscilla Kincaid-Smith, University Department of Medicine, Royal Melbourne Hospital, P.O. 3050, Victoria, Australia.

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