THE PATHOGENIC ROLE OF FIBRIN DEPOSITION IN THE GLOMERULAR LESIONS OF TOXEMIA OF PREGNANCY*

By PIERRE VASSALLI, M.D., ROBERT H. MORRIS,‡ M.D., and ROBERT T. McCLUSKEY, M.D.

(From the Department of Pathology and the Department of Obstetrics and Gynecology, New York University School of Medicine, New York)

Plates 45 to 47

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Glomerular damage constitutes the most constant and one of the most important pathologic features in toxemia of pregnancy. The histologic abnormalities most often described are swelling of glomerular cells, especially the endothelial cells (1). Less commonly, more severe lesions are seen characterized by fibrinoid deposits along the basement membrane (2), or fibrin thrombi within glomerular capillaries (3). In rare instances widespread glomerular thrombosis and cortical necrosis develop; this picture is most often seen in cases complicated by abruptio placentae.

In recent years the nature of the glomerular abnormalities has been clarified by electron microscopic studies. The characteristic findings are marked endothelial swelling, widening of intercapillary spaces, and the frequent occurrence of deposits along the basement membrane of dense, granular material (2, 4–8). Such deposits are generally not visible by light microscopy. Similar glomerular lesions have been observed in rabbits in which a state of intravascular coagulation was induced (9). The glomerular changes ranged in severity from those showing only endothelial and intercapillary cell swelling to those with complete glomerular thrombosis and cortical necrosis. All of the lesions were shown to be the result of the arrest in glomeruli of some form of circulating fibrin. These observations suggested that accelerated intravascular fibrin formation might account not only for the severe renal lesions of pregnancy, but also for the abnormalities most commonly encountered in toxemia.

The present study was undertaken to determine whether an abnormal concentration of fibrin was present in the glomerular lesions of toxemia of pregnancy.

Materials and Methods

Patients.—The patients were from the obstetrical service of Bellevue Hospital (III Surgical Division). The diagnosis of toxemia was based on the development of persistent proteinuria

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and elevation of the blood pressure in the third trimester of pregnancy in the absence of evidence of urinary tract infection, previous hypertension, or renal disease. The patients who served as controls lacked these findings. Proteinuria was determined qualitatively on the first urine voided in the morning. The clinical findings are summarized in Tables I and II.

TABLE I

Toxemic Patients

Patients	Age	Parity	Time of biopsy	Proteinuria	Blood pressure*	Glomerular abnormalities in histologic section	Immunofluorescent staining for			
							Fibrin	γ-Globulin	Albumin‡	β_{1C}
1	22	0	A.P. 39 wks.	+	130/90	Present	+++	0	0	0
2	23	3	A.P. 35 wks.	++	150/100	§	+	0	0	0
			P.P. 3 days			§	+	0	0	0
3	22	0	A.P. 37 wks.	+	140/90	Equivocal	+	0	0	0
4	20	0	A.P. 42 wks.	++++	140/90	§	+++	0	0	0
5	26	2	A.P. 35 wks.	+++	150/98	§	+++	0	+	0
			A.P. 38 wks.‖			Present	+++	+	+	0
6	26	0	A.P. 33 wks.	++++	148/100	Present	+++	+	+	0
			P.P. 7 days			§	+	±	+	0
7	18	0	A.P. 28 wks.	+++	144/96	Present	+++	0	+	0
8	18	0	A.P. 25 wks.	++	150/100	Present	+++	0	0	0
9	23	0	P.P. 1 day‖	++	140/100	§	++	0	0	0
10	18	0	A.P. 36 wks.	+++	150/100	Present	+++	+	+	0
11	24	3	A.P. 30 wks.‖	+++	200/130	§	+++	0	0	0

A.P., antepartum; P.P., postpartum.

* Refers to highest blood pressure reading.

‡ Refers to droplets in glomerular epithelial cells.

§ Tissue not available for histologic sections.

‖ Stillborn.

Processing of Tissue.—Renal biopsy was performed percutaneously using a modified Franklin Vim Silverman needle. The biopsy specimen was divided into 2 pieces; one piece was frozen and if it was found to contain glomeruli on frozen section, the other portion was fixed in Bouin's solution. The tissue fixed in Bouin's for histological examination was sectioned at 1 to 2 micra and stained with hematoxylin and eosin, PAS, azancarmine, PAS silver methenamine, and phosphotungstic acid hematoxylin (PTAH). The portion to be frozen was

inserted into a small slit made in a block of fresh rabbit liver and frozen by CO_2 gas on a freezing stage.

Specimens were sectioned immediately at 4 micra in an International-Harris cryostat and were stained the same day or were stored at −20°C until stained. It was found that storage under these conditions did not lead to appreciable loss of specific staining during a period of several weeks. Sections were fixed in acetone for 10 minutes and washed for 5 minutes in 0.15 M saline containing 0.02 M phosphate buffer at pH 7.0. The sections were covered with

TABLE II

Control Patients

Patients	Age	Parity	Time of biopsy	Proteinuria	Blood pressure	Clinical data	Pathologic findings in histologic sections	Immunofluorescent staining for	
								Fibrin	γ-Globulin
12	33	2	A.P. 37 wks.	0	114/75	Normal pregnancy	Absent	0	0
13	21	2	A.P. 35 wks.	0	110/80	Normal pregnancy	Absent	0	0
14	18	0	A.P. 38 wks.	+	120/80	Urinary tract infection	Focal lymphocytic infiltration	0	0
15	21	0	P.P. 4 days	+	105/60	Urinary tract infection	*	0	0
16	34	8	P.P. 3 days	0	140/80	Probable hypertensive disease	Arteriolar changes compatible with hypertensive disease	0	0
17	30	4	P.P. 4 days	0	110/70	Normal pregnancy	*	0	0

A.P., antepartum; P.P., postpartum.

* Tissue not available for histologic section.

the conjugated antiserum for 30 minutes in a moist chamber at room temperature, followed by 2 washes of 5 to 10 minutes in buffered saline. The tissues were examined by a Zeiss standard microscope used with an Osram HBO 200-watt lamp and a darkfield immersion condensor. The frozen sections contained between 3 and 10 glomeruli.

Antisera.—Antiserum to human fibrinogen was prepared by immunizing rabbits with human fraction I. The serum was repeatedly absorbed with human serum until it showed a single line by the Ouchterlony method against human plasma and none against human serum.

Rabbit anti-human γ-globulin serum was obtained from Antibodies, Inc. (Davis, California). The antiserum was repeatedly absorbed by a fraction of human serum from which

γ-globulin had been removed by sodium sulfate precipitation. Following absorption the antiserum produced a single line against human γ-globulin in double diffusion in agar and a characteristic γ-globulin line in immunoelectrophoresis.

Rabbit anti-human albumin was obtained from Antibodies, Inc. By immunoelectrophoresis this serum showed a strong line against albumin and a very faint line against an α-globulin.

Rabbit anti-human β_{1C} and β_{1A} was generously provided by Dr. Müller-Eberhard (10). This serum showed in immunoelectrophoresis a strong line against β_{1C} and a faint line against β_{1A}.

Conjugation.—The antisera were conjugated with fluorescein isothiocyanate on Celite 10 per cent (California Corp. for Biochemical Research, Los Angeles) according to the method of Rinderknecht (11). Following conjugation the sera were centrifuged for 30 minutes at 15,000 RPM at 5°C, and then dialyzed for several days at 4°C against 0.005 M phosphate buffer at pH 8.1. The background staining was of such low intensity that it was not necessary to remove non-specific staining. The conjugated anti-β_{1C} was shown to give definite but faint glomerular staining in several cases of acute glomerulonephritis and lupus nephritis (12). The specificity of the fluorescent staining for fibrinogen antigenic determinants was shown by the complete abolition of staining by absorption of the conjugated serum with a highly purified human fibrinogen kindly provided by Dr. Alan Johnson (13). The specificity of the staining for γ-globulin was demonstrated by the complete removal of staining by absorption of the conjugated serum by human fraction II.

RESULTS

The pertinent clinical data and the results of histologic and immunofluorescent studies are shown in Tables I and II. Of the biopsies from the toxemic patients, material from 7 was processed by regular histologic methods. In 6 of these patients, glomerular abnormalities were found and in the other only equivocal changes were present. The changes were not so distinctive as to be considered as diagnostic, but they resemble those previously described by others (1). The glomeruli tended to fill Bowman's space, the endothelial cells and intercapillary cells were swollen, and the capillary lumens narrowed (Fig. 1). Swelling of epithelial cells was also seen and these occasionally contained eosinophilic, PAS-positive droplets. Equivocal endothelial cell proliferation was present in 2 cases. In 2 cases PAS silver methenamine sections showed abundant finely fibrillar silver staining material in the intercapillary regions and between endothelial cells; in some areas the fibrils gave the appearance of duplication of the basement membrane (Fig. 2). In the 4 instances in which only frozen sections were available, evaluation of endothelial swelling was not possible.

In none of the cases were severe changes encountered and in particular no glomerular thrombi, fibrinoid deposits, or deposits of material with the staining properties of fibrin were seen. Sections from control patients showed no abnormalities, except for focal interstitial lymphocytic infiltration in one case, and arteriolar thickening in another.

In the sections exposed to conjugated anti-fibrin serum, bright staining of glomeruli was seen in all of the biopsies from patients with toxemia. Except in one case, all the glomeruli were stained to a fairly uniform extent. The staining involved the entire glomerulus and appeared to be within endothelial cells and intercapillary cells (Figs. 3 and 4). Occasionally, there was deposition of brightly staining material which appeared to lie along the basement membrane. Fibrin was not clearly demonstrated

within glomerular epithelial cells, although the presence of some material in this location could not be excluded. Fibrin thrombi were not identified within glomerular capillaries. In most cases, the glomerular staining was so bright that these structures stood out clearly at low magnification (about 32 ×). The glomerular staining was arbitrarily graded as 1, 2, or 3+. In one case, a single glomerulus showed virtually no staining, whereas the others were brightly stained. In material from both control and toxemic groups, faint to moderate staining was seen in many intertubular capillaries. In two instances, repeat biopsies were performed postpartum, at 4 and 7 days, and it was found that the glomeruli still contained fibrin, although less than during pregnancy. It is known from electron microscopic studies that the glomerular lesions only slowly involute following delivery (2).

Biopsies were performed in 6 control patients. Three were done before delivery and 3 within 4 days following delivery. Only very faint glomerular staining was seen (Fig. 5), which, however, was not present in tissue stained with conjugated antiserum previously absorbed with human fibrinogen, indicating that small amounts of fibrinogen or fibrin were present within these glomeruli.

Examination of the biopsies for γ-globulin showed significant staining in only 3 toxemic patients and in none of the controls. The γ-globulin was seen in the form of irregular deposits along the basement membrane (Fig. 6). Deposits of fibrin with the same distribution were seen in these cases. In one instance, the γ-globulin was seen only in a repeat biopsy performed 3 weeks after the first, and the material was irregularly distributed among and within glomeruli. In several cases in both groups there was observed a faint, very thin line of staining for γ-globulin apparently along the basement membrane, the significance of which is unknown.

Biopsies were examined for albumin and β_{1C} only in the toxemic group. Sections stained for albumin failed to show staining in glomeruli except for 3 cases, in which bright granules were seen in epithelial cells. In 3 cases with marked proteinuria, numerous, brightly stained droplets were present within the cytoplasm of tubular cells. In sections stained for β_{1C} no staining was observed.

DISCUSSION

In the present study, a striking concentration of fibrin or other materials derived from fibrinogen[1] has been demonstrated by immunofluorescence in the glomeruli of patients with toxemia of pregnancy. In contrast, gamma globulin was only occasionally demonstrable and was present in smaller amounts and in a different distribution. β_{1C}, a constituent of complement, was not observed in glomeruli. Albumin was only rarely seen, and then in the form of droplets within epithelial cells. In pregnant patients without toxemia only very faint staining for fibrin was observed in glomeruli.

Fibrin was distributed fairly uniformly throughout glomeruli and was deposited within endothelial and intercapillary cells; swelling of these cells

[1] For convenience, material stained by the anti-fibrin serum will be referred to as fibrin, although it is most likely that the stained material largely represents some derivative of fibrinogen, as will be discussed.

constituted the major pathologic change seen in histologic sections. The consistent presence of fibrin and its wide distribution in glomeruli indicate that the material stained did not correspond only to the abnormal deposits frequently observed by electron microscopy in this condition. However, in three cases fibrin was observed not only diffusely within cells but also in the form of deposits which followed the basement membranes.

The results of immunofluorescent staining of glomeruli in toxemia appear to be different from those observed in any other glomerular disease. Marked accumulation of fibrin may occasionally be demonstrated in glomeruli in acute glomerulonephritis, or lupus nephritis (12), but in these conditions the material is less regularly distributed within and among glomeruli. Furthermore, in these situations, striking accumulation of gamma globulin along the basement membrane is observed, as well as some β_{1C}. The absence of gamma globulin in glomeruli in most cases of toxemia and the lack of complement provide strong evidence against the suggestion that the glomerular lesions have an immunologic basis (14). The significance of the occasional presence of irregular deposits of gamma globulin is not clear, but they seem to be associated with unusually large deposits of fibrin along the basement membrane. It is possible that this represents trapping of gamma globulin in fibrin deposits.

The presence of fibrin within glomeruli has been reported previously in certain complications of pregnancy. However, in contrast to the present observations, such reports have been concerned with patients with eclampsia, abruptio placentae, or with toxemia complicated by abruptio placentae, and the fibrin was apparent in histologic sections as intraluminal deposits. In these conditions, there is evidence for the existence of a state of intravascular clotting. In many cases, widespread deposits of fibrin have been observed within small vessels of many organs, such as liver, lungs, adrenals, hypophysis, brain (3, 15, 16), and particularly in glomeruli, where large occlusive fibrin masses are frequently associated with renal cortical necrosis (3). An immunofluorescent study of one such case has confirmed that the deposits are composed largely of fibrin (17). These conditions are often accompanied by a hemorrhagic state which is characterized by depression of circulating fibrinogen, platelets, and other clotting factors and which is generally believed to be due to the consumption of clotting factors resulting from extensive intravascular coagulation (15, 18, 19). This is sometimes associated with an excessive fibrinolytic response, in which case the hemorrhagic state is accentuated and the fibrin deposits may be prevented. It has been proposed that these complications are initiated by release of thromboplastin secondary to placental abnormalities (15, 18). It is possible to extract from placental tissue a thromboplastic material which, when injected into experimental animals, results in fibrin deposition with hepatic lesions similar to those observed in eclampsia and in clotting abnormalities comparable to those mentioned above (15, 18). It has since

been demonstrated that intravenous injections of thrombin can also lead to renal cortical necrosis (20, 21). Evidence that renal cortical necrosis complicating pregnancy is the result of a state of intravascular clotting has been reviewed elsewhere (22). The resemblance of the lesions of these severe complications of pregnancy to those of the generalized Shwartzman reaction, which was pointed out by McKay (3), can be understood in the light of the knowledge that this experimental disease is the consequence of intravascular coagulation (23).

The clinical course and morphologic features of uncomplicated toxemia do not suggest that this condition has a pathogenic mechanism similar to that responsible for the acute complications just discussed. However, the demonstration in the present study of large amounts of fibrin in glomeruli in toxemia provides a link between these conditions.

It is proposed that the glomerular lesions of toxemia represent a reaction to some form of circulating fibrin which is arrested in glomeruli, and it is suggested that this could be the result of a prolonged state of slow intravascular coagulation. It has been shown experimentally that the infusion of thromboplastin into rabbits can result in glomerular lesions characterized ultrastructurally by endothelial swelling and deposits similar to those seen in toxemia (9, 24). It was shown that the dense granular material forming these deposits, which is sometimes referred to as fibrinoid (2), was derived from fibrin and that the endothelial swelling was a consequence of phagocytosis of fibrin. Endothelial swelling was sometimes observed even when fibrin or fibrinoid were not demonstrable by electron microscopy, and evidence was presented indicating that this represented a reaction to ingestion of some form of fibrin precursor (9, 24). Shainoff and Page have recently shown that the fibrin monomer may combine with native fibrinogen to form a complex referred to as cryoprofibrin (25). With slow coagulation, this material may be formed in the absence of fully polymerized fibrin (25). Cryoprofibrin appears in the circulation when intravascular coagulation occurs and is considered to be the most sensitive indicator of the action of thrombin on fibrinogen *in vivo* (26). It appears that the material referred to as heparin-precipitable fibrinogen (27), which is present in the blood of rabbits perfused with thrombin (20), represents cryoprofibrin (25, 26). Thus, with slow intravascular coagulation, cyroprofibrin and perhaps other abnormal complexes derived from fibrinogen are present in the circulation.

It is known that glomerular damage can result from deposition of circulating colloidal material, and, in many such instances, no obvious pathologic changes are seen in other sites (28). When colloidal material is present in the circulation, most of it is cleared by the reticuloendothelial system; these phagocytic cells quickly degrade the material, in most instances, without apparent damage. In contrast, glomeruli take up circulating colloidal material at a much slower

rate but show progressive accumulation of such material, associated with the development of glomerular damage (29). Evidence that products derived from fibrinogen in the course of intravascular coagulation are removed by the reticuloendothelial system has recently been obtained (30). The glomerular lesions of toxemia would appear to represent a reaction to circulating colloidal material derived from fibrinogen.

Although no conclusive evidence of a state of accelerated intravascular clotting in toxemia has been presented, several observations have been reported which can be interpreted in this way. These include prolongation of clotting time, thrombin time (31), and thrombocytopenia (31, 32), which is known to be a sensitive indicator of intravascular clotting. Of particular interest is the observation of Smith that unusually high levels of heparin-precipitable fibrinogen occur in toxemia of pregnancy (33). The consequence of slow intravascular clotting may be accentuated by impairment of fibrinolytic mechanisms, which is known to occur during pregnancy (34).

That toxemia is the result of the release of noxious substances from the placenta is an old and widely held concept. Excessive degenerative changes of the placenta have been described as characteristic of toxemia (35, 36). It has been proposed that these changes may be responsible for the release of thromboplastic substances of the placenta, and that this could play a role in the pathogenesis of toxemia (35, 37). It is possible that placental abnormalities could result in the prolonged release of small amounts of thromboplastin. Thus, all of the complications of pregnancy which have been mentioned above may be due to intravascular coagulation resulting from placental abnormalities which occur at different levels of intensity and for different periods of time. Depending upon these factors, and on the fibrinolytic response, there would result a whole range of glomerular lesions varying from simple endothelial swelling to complete glomerular thrombosis, and a variety of clinical states. It is not surprising that the acute complications occur with greater frequency in the face of previous placental damage associated with toxemia, nor, on the other hand, that such states could arise *de novo* as the result of some acute placental catastrophe.

There are indications that even in the course of normal pregnancy, slow release of placental thromboplastin may occur at a low level. Peculiarities of the clotting system have been described, which have been referred to as a "hypercoagulable state" (38), and elevations of heparin-precipitable fibrinogen have been observed, but not to the levels seen in toxemia (33). In the present study, the impression was obtained that the glomeruli of patients with normal pregnancy showed an equivocal increase in fibrin as compared with normal non-pregnant patients (12).

The glomerular reaction to circulating fibrin could explain most of the clinical features observed in toxemia. However, a variety of other mechanisms

undoubtedly play a role in the toxemic state. Some of these may result from intravascular coagulation in ways other than an effect on glomeruli, for example by a release of vasoactive materials resulting from the action of thrombin on platelets (39) and fibrinogen (40).

The demonstration, in the present study, of fibrin in glomeruli of patients with toxemia, the production of glomerular lesions resembling those seen in toxemia by thromboplastin infusions in rabbits, and the observations indicating clotting abnormalities in toxemia, provide strong evidence that the basic pathogenic mechanism accounting for the renal lesions of toxemia is the reaction of the glomerulus to the arrest of some form of circulating fibrin.

SUMMARY

An immunofluorescent study of renal biopsies from patients with toxemia of pregnancy has been performed. It was found that the glomeruli consistently showed bright staining for fibrin within endothelial cells, as well as occasional deposits along the basement membrane. Gamma globulin was only occasionally demonstrable, generally in the form of irregular deposits along the basement membrane. β_{1C} was absent and albumin was not seen in glomeruli, except sometimes in the form of droplets within epithelial cells.

In biopsies from pregnant patients without toxemia only equivocal staining for fibrin was seen.

On the basis of these observations and other evidence discussed, it is proposed that the accumulation of fibrin in glomeruli reflects a prolonged state of intravascular clotting in toxemia and that the arrest in glomeruli of some form of circulating fibrin constitutes the basic pathogenic mechanism of the glomerular damage in this disease.

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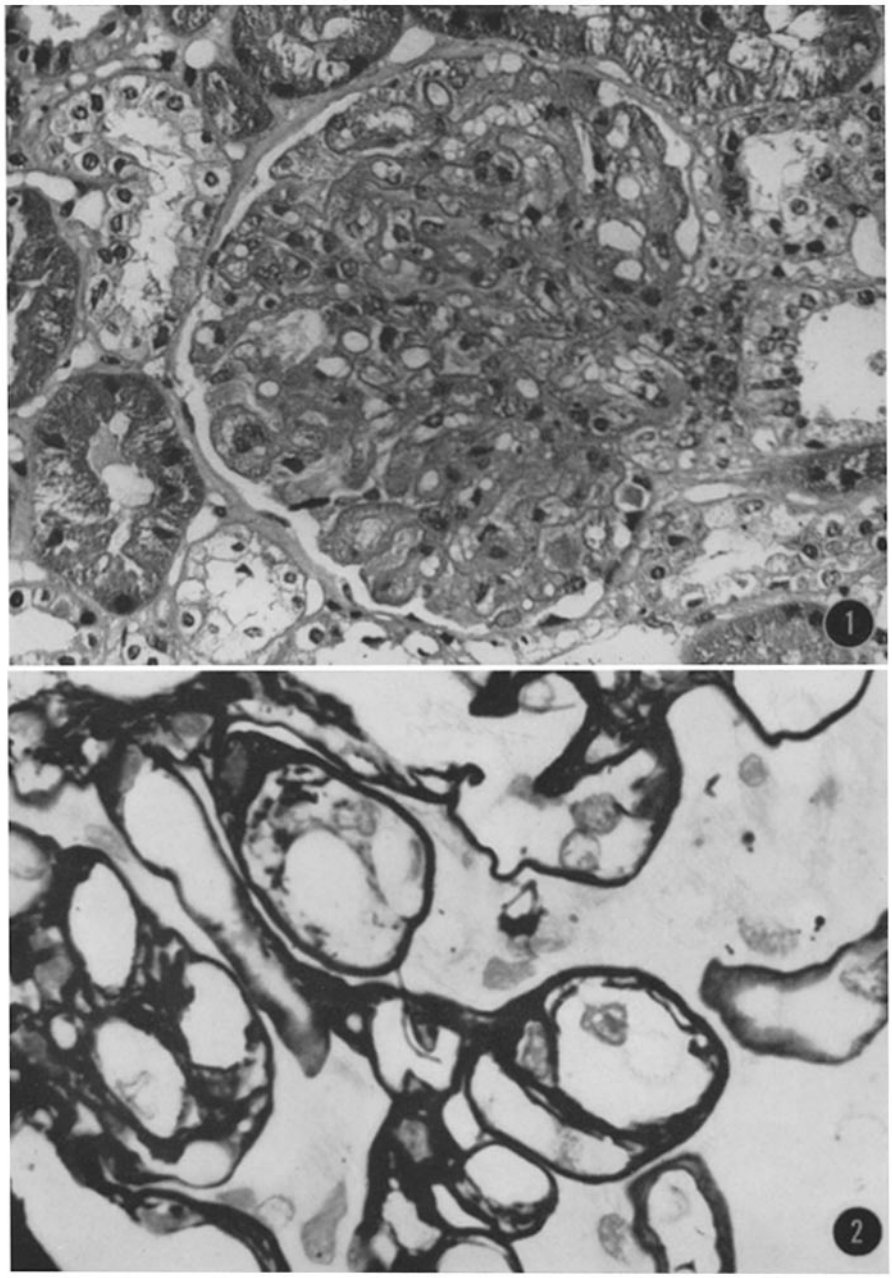
EXPLANATION OF PLATES

PLATE 45

FIG. 1. Glomerulus from toxemic patient No. 7 showing swelling of cells and enlargement of the glomerulus. Hematoxylin and eosin. × 700.

FIG. 2. Portion of glomerulus from patient No. 5 shows increase in silver positive fibrillar material which produces apparent duplication of the basement membrane in one area. PAS silver methenamine. × 2200.

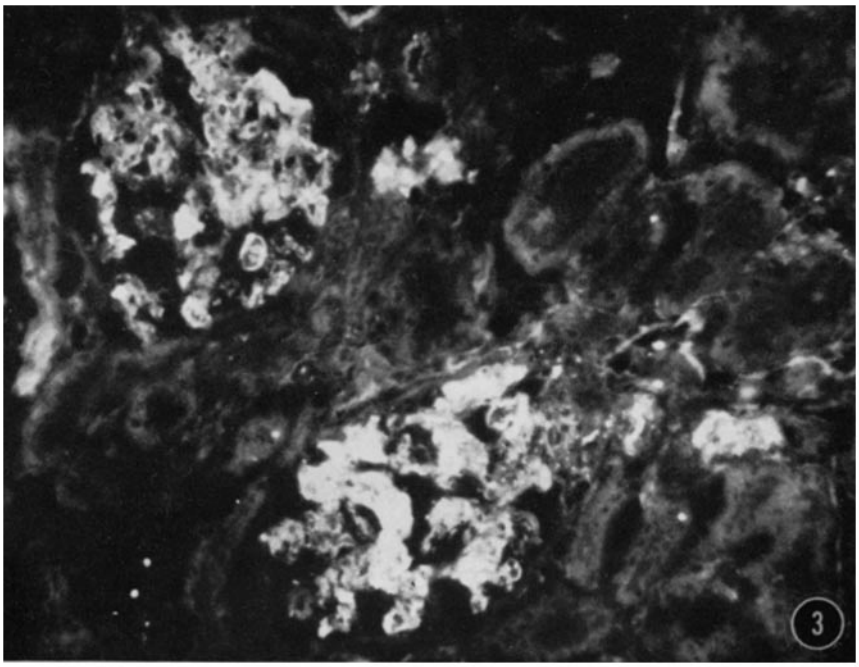


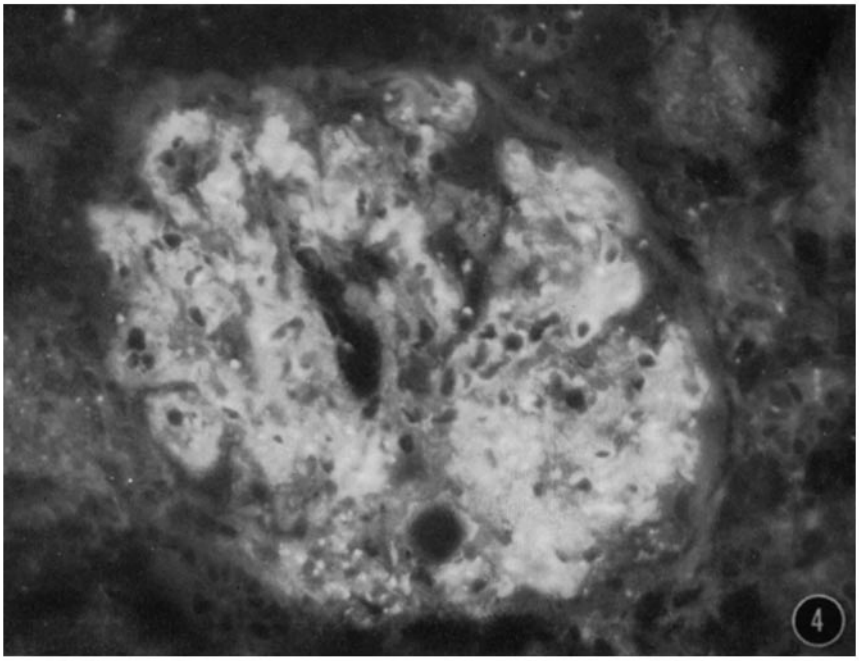
(Vassalli *et al.*: Pathogenic role of fibrin deposition)

PLATE 46

FIG. 3. Biopsy from toxemic patient No. 5 stained with anti-fibrin serum. Two brightly stained glomeruli are seen. The bright material to the left of the lower glomerulus represents blue autofluorescent material. The bright area to the left of the upper glomerulus represents specific fluorescence in the lumen of a small blood vessel. × 360.

FIG. 4. Glomerulus from toxemic patient No. 4 showing bright staining for fibrin within swollen endothelial and intercapillary cells. × 700.



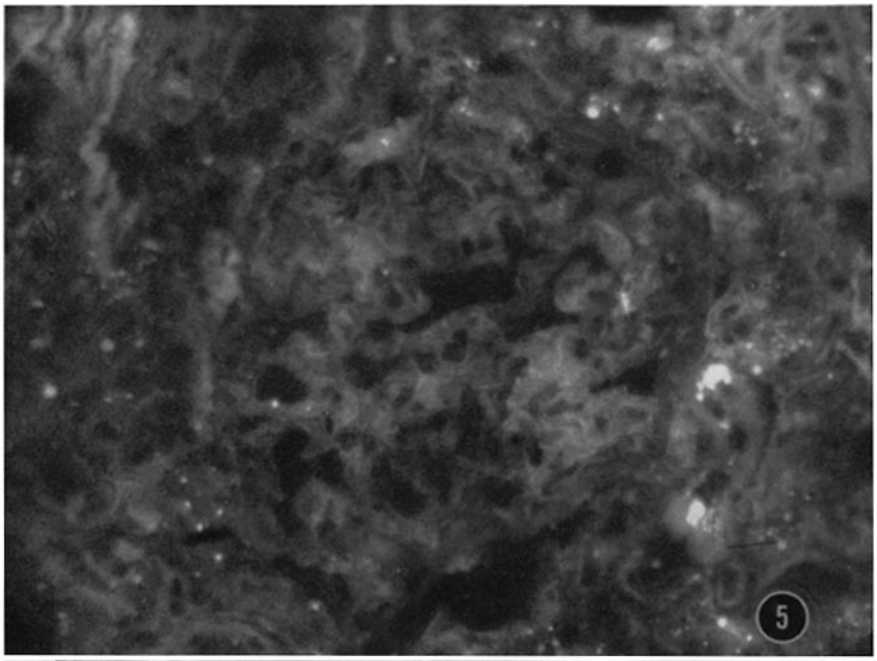


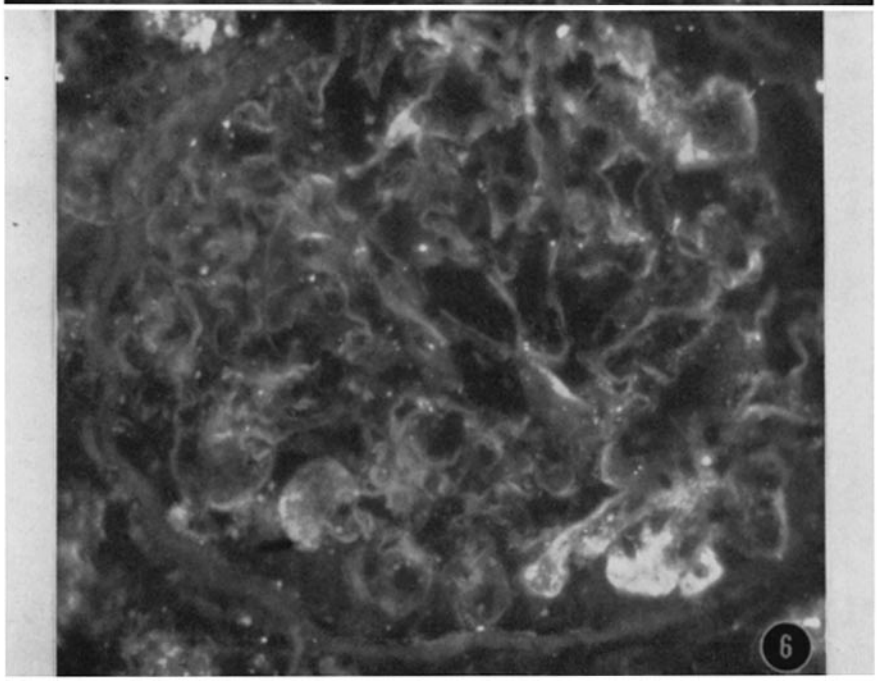
(Vassalli *et al.*: Pathogenic role of fibrin deposition)

PLATE 47

FIG. 5. Glomerulus from control pregnant patient No. 12 showing extremely faint specific staining for fibrin in glomerulus. The bright granules outside the glomerulus are artefacts. × 650.

FIG. 6. Glomerulus from toxemic patient No. 6 exhibiting moderately bright staining for γ-globulin in the form of deposits outlining basement membrane. This illustrates the maximal amount of staining for γ-globulin which was seen. The thin line of specific staining seen throughout the glomerulus was also seen in normal glomeruli. × 1000.





(Vassalli *et al.*: Pathogenic role of fibrin deposition)