Virchows Arch. A Path. Anat. and Histol. 367, 171—179 (1975)
© by Springer-Verlag 1975

Late Changes of Irreversible Post-Partum Renal Failure

Per Henrik Becher Carstens and R. Karalakulasingam
Departments of Pathology and Medicine, University of Louisville School of Medicine, Louisville, Kentucky

Received April 3, 1975

Summary. The clinico-pathological data from a patient with irreversible post-partum renal failure (IPRF) are presented. The electron microscopy of the late changes are described for the first time and consists of: *1.* Thickening of the basement membrane. *2.* Interposition of mesangial cells and matrix between the thickened basement membrane and the endothelial cell encircling the periphery of the tuft. *3.* Multiplication of basal lamina material between mesangial cells and endothelial cells. *4.* Proliferation of endothelial cells.

All of the above changes tend to obliterate the glomerular tufts and transform the vascular lumina into slit-like spaces. They explain morphologically why most patients with IPRF terminate in chronic renal failure, if they survive the early changes. The late occurring hypertension is regarded as a secondary stimulation of the renin-angiotension system caused by partial or complete occlusion of arteries and arterioles.

Key words: Kidney failure — Pregnancy — Electron microscopy — Hemolytic-uremic-syndrome — Basement membrane — Endothelium.

Introduction

Irreversible post-partum renal failure (IPRF) is considered to be a sub-group of the adult hemolytic-uremic syndrome (Lawrence *et al.*, 1973). IPRF usually occurs in a multiparous patient within days or weeks after a normal delivery. No prior preeclampsia or renal disease is evident. The majority of patients will without major prodromal symptoms develop microangiopathic hemolytic anemia and oliguria leading rapidly into renal failure. If the patient survives the acute stage, hypertension invariably occurs, and other organ systems may be involved.

The etiology is unknown and both infections (viral) and drugs (ergot preparations and antibiotics) have been incriminated. The pathological findings on both biopsy and autopsy material are constant. In the acute state marked fibrin deposits in small arterioles associated with fibrinoid necrosis of the vessel wall are seen. There is no inflammatory reaction. With progression of the disease, the vascular lumina becomes occluded by concentric layers of loose connective tissue. The disease involves the glomeruli as evidenced by fibrinoid necrosis and thickening of the basement membranes.

Twenty five patients with IPRF have been reported in the literature, if patients with renal symptoms prior to the post-partum period are excluded (Sheer and Jones, 1967; Robson *et al.*, 1968; Wagoner *et al.*, 1968; Rosenmann *et al.*, 1969; Clarkson *et al.*, 1969; Ogg and Cameron, 1969; Churg *et al.*, 1970; Luke *et al.*, 1970; Ponticelli *et al.*, 1972; Eisinger, 1972; Epstein and Scully, 1973; Larcan *et al.*, 1974; Donadio and Holley, 1974; Finkelstein *et al.*, 1974). Only nine patients had the renal tissue examined with the electron microscope (Sheer and Jones, 1967; Robson *et al.*, 1968; Rosenmann *et al.*, 1969; Larcan *et al.*, 1974;

Donadio and Holley, 1974; Finkelstein *et al.*, 1974). All nine patients were in the early stage, whereas this case represents the late stage and sheds some light on the irreversible changes that lead to permanent renal failure.

Material and Methods

Two kidney biopsies were performed, 48 and 98 days after the initiation of renal symptoms. Both biopsies were submitted for light as well as electron microscopy. Immunofluorescent studies were unfortunately not performed. The tissue from the first kidney biopsy submitted for electron microscopy did not contain any cortical tissue.

For light microscopy, tissue was fixed in 10% formalin. Paraffin sections were stained with hemotoxylin and eosin, periodic acid-Schiff (PAS), periodic acid-silver methenamine (PASM) and phosphotungstic acid-hematoxylin (PTAH). For electron microscopy, tissue was fixed in 3% glutaraldehyde. The tissue was postfixed in osmium tetroxide, dehydrated in graded ethanols and embedded in Maraglas. Thick sections were stained with toluidine blue. Thin sections were cut with an ultratome, stained with uranyl acetate and lead citrate, and examined with a Siemens Elmiskop I electron microscope.

Case Report

A 22-year-old black female admitted at term had experienced three previously normal pregnancies without toxemia or renal disease. At the time of admission, all physical findings and laboratory tests were within normal limits.

On 10/15/1973 the patient delivered a male infant without difficulty. The next day a tubal ligation was performed. The patient received ergometrine postoperatively. Six hours postoperatively a massive intra-abdominal hemorrhage occurred associated with hypotension. Exploratory laparotomy was performed and 2000 cc. of blood was found in the abdominal cavity. The cause of the bleeding was a slipped ligature at the site of the right salpingectomy. She was transfused with three units of whole blood, same blood type as the patient and properly cross matched, without any apparent reactions. Following whole blood transfusion, her hemoglobin was 10 grams per cent, hematocrit 29.8 per cent. Seventy-two hours later the patient was noticed to be jaundiced, anemic and oliguric. Hemoglobin was 6.6 grams per cent with a hematocrit of 20.4 per cent. Platelet count was 36000, reticulocyte count 5.4 per cent, urea nitrogen 36 mg, creatinine 2.8 mg, bilirubin 5 mg (indirect 4 mg). The fibrinogen titer was 0.78, test for fibrin split products was negative, bleeding and clotting times were normal. Peripheral blood film was not evaluated for schistocytes. She was treated with 12.5 grams of Mannitol IV following which she had a massive diuresis of three liters in 24 hours. She continued to remain in the diuretic phase over the next two weeks and the urea nitrogen and the creatinine progressed to values of 240 mg and 17.5 mg respectively. The patient was treated with restricted protein diet.

On November 29, the patient became hypertensive for the first time. Her blood pressure was 150/110 but blood pressure control was maintained adequately with Reserpine injection and subsequently with Aldomet. On December 10, she became markedly hypertensive with a blood pressure of 230/150. It was controlled with great difficulty using Guanethidine 50 mg, Aldomet 2 grams and Hydralazine 300 mg daily. By December 20, exudates and hemorrhages were present in both fundi and she was started on intermittent hemodialysis using an external shunt. The patient is now on permanent hemodialysis thrice weekly and adequate blood pressure control has been maintained with Aldomet 2 grams and Hydralazine 300 mg daily.

Light Microscopy. Two kidney biopsies were performed on this patient, (December 4th and January 23rd, 48 and 98 days after the onset of renal symptoms. The first biopsy showed glomerular hypercellularity, mainly of endothelial and mesangial cells with diffuse thickening of the basement membrane.

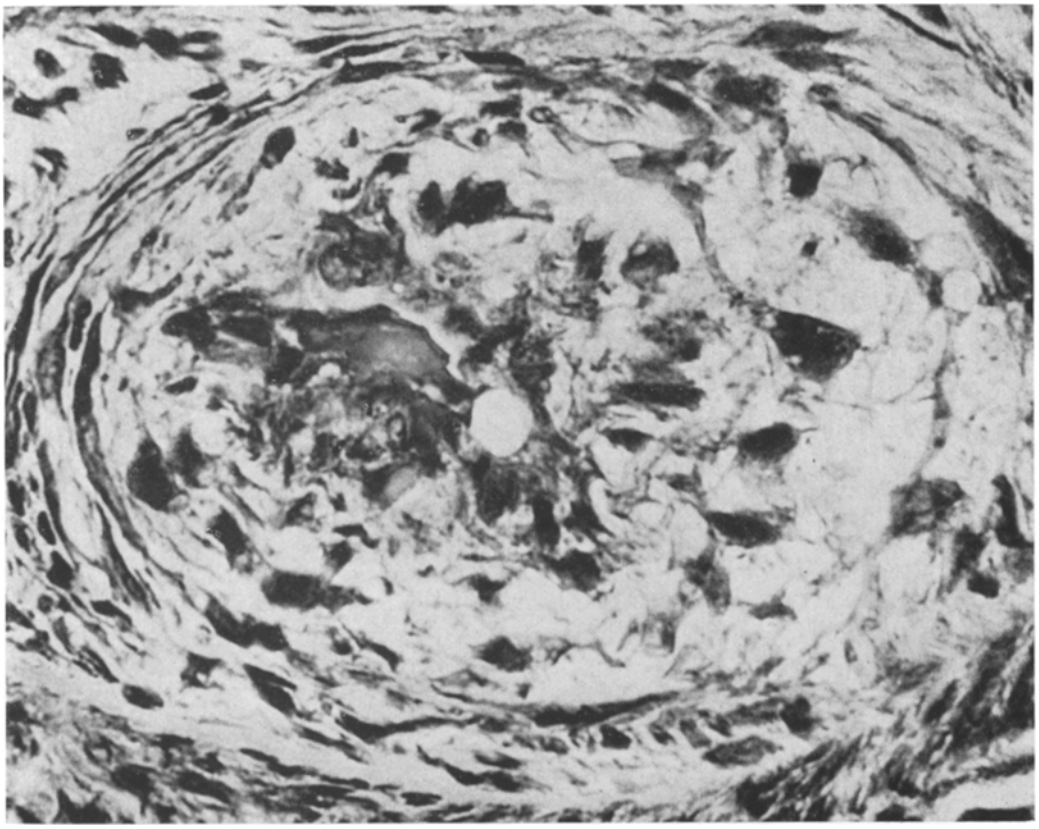

Fig. 1. Arteriole showing fibrinoid necrosis and subendothelial fibrindeposit. First kidney biopsy. Phosphotungstic Acid-Hematoxylin (× 600)

Interlobular arteries and arterioles showed evidence of fibrinoid necrosis and subendothelial fibrindeposits (Fig. 1).

In the second biopsy hypercellularity of the glomeruli was still present. Several tufts were, however, completely obliterated by dense amorphous hyaline material (Fig. 2). Striking changes were noted in both the interlobular arteries and the arterioles. Most arteries were occluded by a concentrically thickened "onion-skin" intima (Fig. 3). Loose, sometimes mucoid, deposits were found in the intima below proliferative endothelial cells. No inflammatory cells were present in or around the vascular structures. The juxtaglomerular apparatus appeared prominent.

Electron microscopy was only performed on the second kidney biopsy. The basement membrane was diffusely and irregularly thickened. The lamina densa varied in thickness and electron-density. It often contained a rarified zone close to the endothelial cells (Fig. 4). There were no electron-dense deposits within any location of the basement membrane. In most tufts, especially the ones where the vascular lumen was greatly reduced, mesangial cells and matrix were inter-

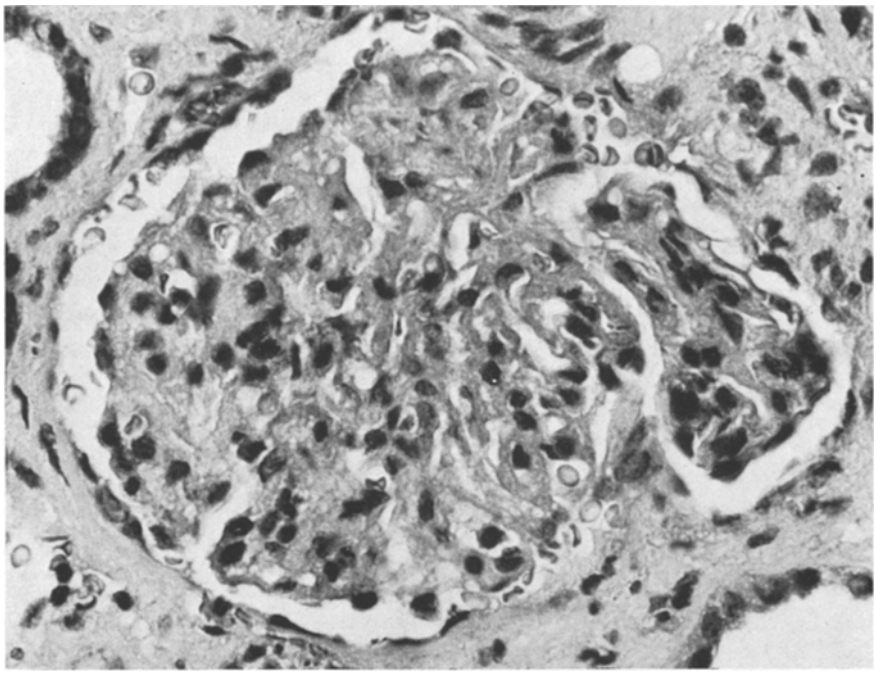

Fig. 2. Hypercellular glomerulus. The vascular tufts are obliterated by amorphous hyaline material, mesangial and endothelial cells. Second Kidney biopsy (×550)

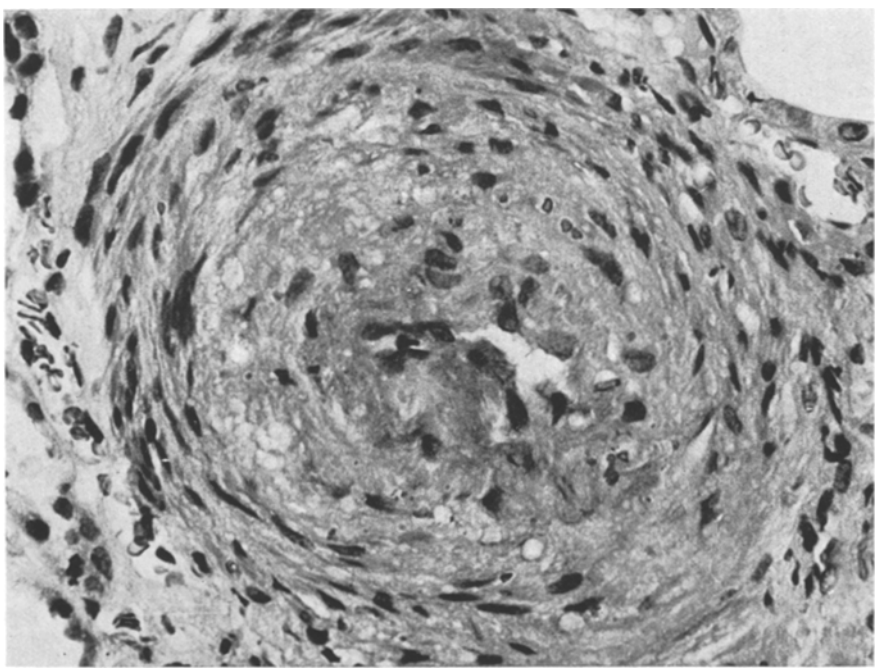

Fig. 3. Interlobar artery. The lumen is almost occluded by loose mucinous subendothelial deposits surrounded by onion-skin proliferation of the media. Second kidney biopsy (×474)

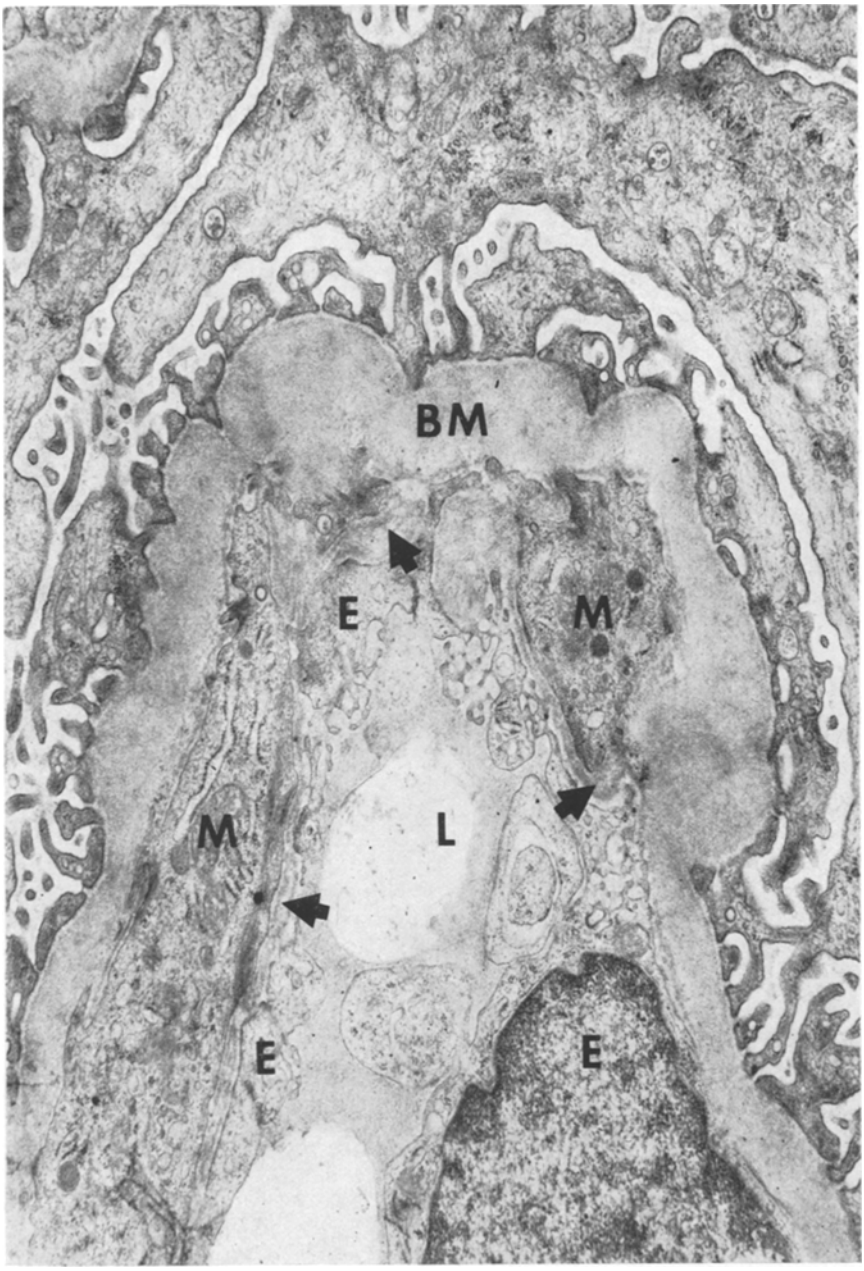

Fig. 4. Electronphotomicrograph of peripheral glomerular tuft. The mesangial cells (*M*) are interposed between the thickened basement membrane (*BM*) and the endothelial cells (*E*). Basal lamina material (arrows) separates the mesangial and endothelial cells. (*L*) indicates the vascular lumen (× 7500)

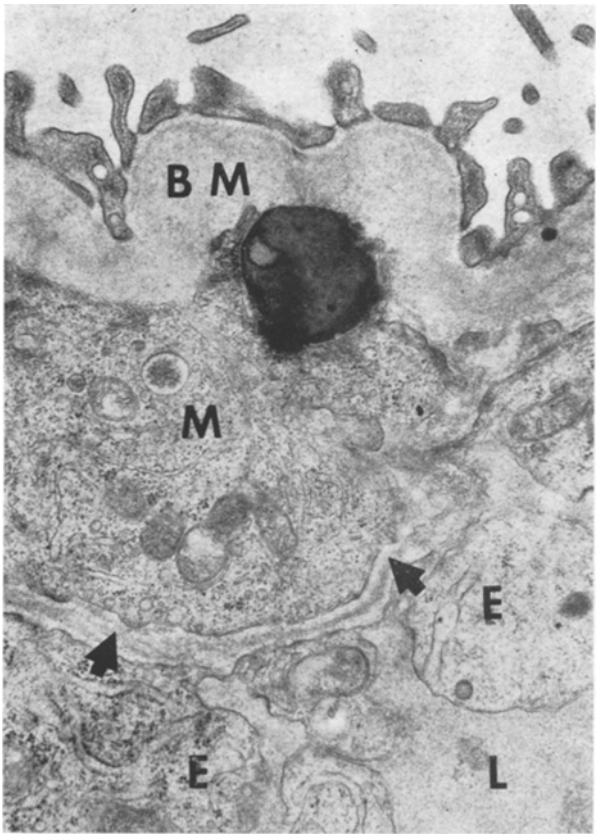

Fig. 5. Electronphotomicrograph of peripheral glomerular tuft. Portion of the mesangial cell (*M*) is surrounding electron dense material in the basement membrane. The mesangial cell (*M*) is interposed between the thickened basement membrane (*BM*) and the endothelial cells (*E*). (*L*) indicates the vascular lumen, (arrows) indicate basal lamina material between mesangial and endothelial cells (× 15000)

posed between the basement membrane externally and the cytoplasm of the endothelial cells internally (Figs. 4 and 5). These interposed mesangial cells would constitute a constricting ring around the whole periphery of the glomerular tuft (Fig. 4), and often surrounded electron dense material in the basement membrane (Fig. 5). Between the interposed mesangial cells and the endothelial cells one or more layers of basal lamina material was noted (Fig. 5). In addition to the above mentioned changes, a proliferation of endothelial cells would further contribute to narrowing of the vascular lumen (Fig. 6).

Some proliferation of epithelial cells was present but in minimal amount and most of the foot processes were of normal configuration without any fusion. The intima of interlobular arteries was thickened by fibroblasts, collagen and cellular debris. The afferent arteriole was similarly changed. A great number of cells in the media of the afferent arteriole contained an abundance of dark crystals presumed to be renin (Fig. 7). No material with the specific periodicity of fibrin was noted.

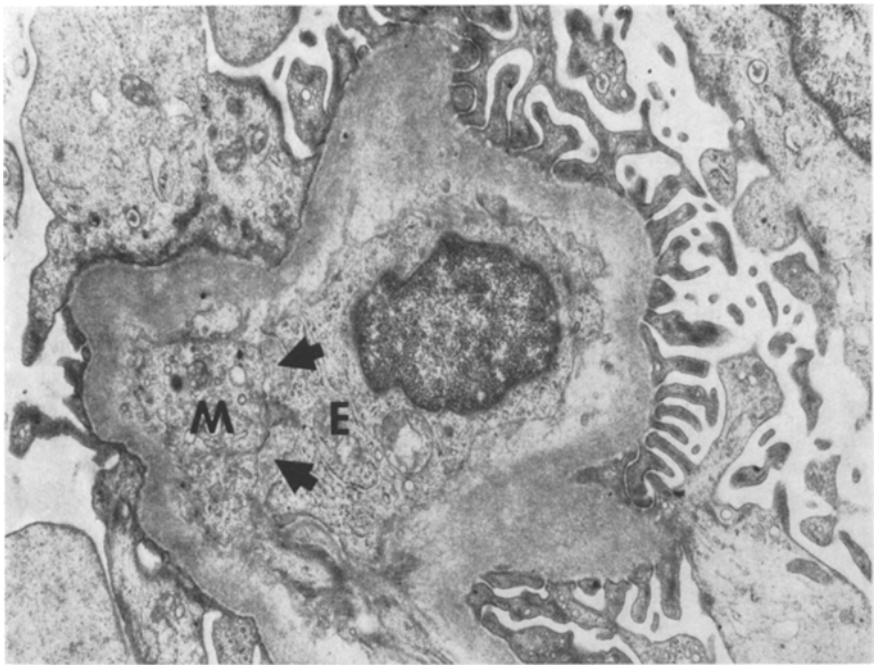

Fig. 6. Electronphotomicrograph of obliterated peripheral glomerular tuft. Multilayered basal lamina material (arrows) is separating the mesangial cell (*M*) and the swollen endothelial cell (*E*) (×5000)

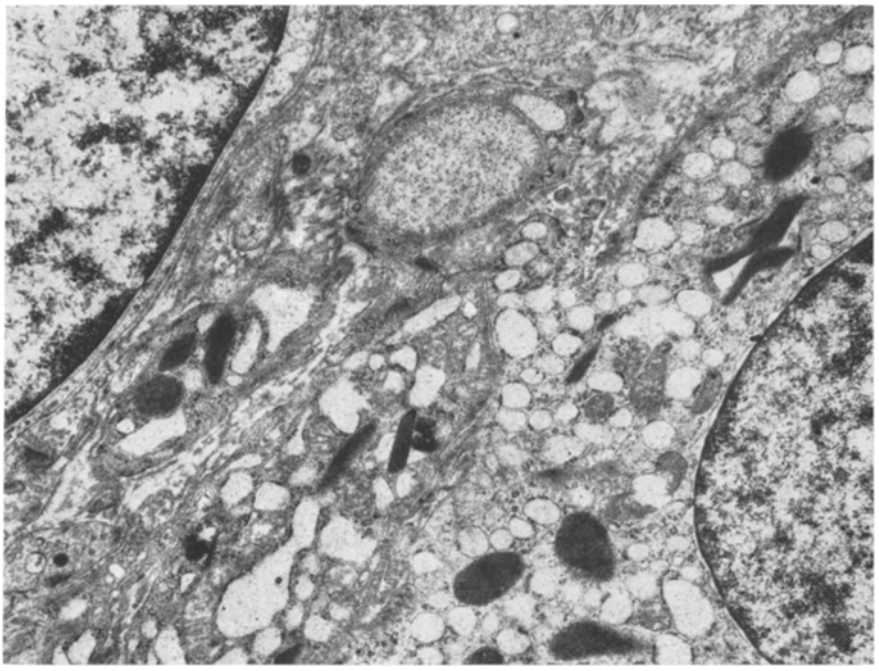

Fig. 7. Electronphotomicrograph of cells from the media of the afferent arteriole containing numerous crystals of various shape (× 7500)

Discussion

Our patient belongs to the group originally described by Robson *et al.* (1968) and termed "irreversible post-partum renal failure" (IPRF). Three days post-partum, she experienced jaundice, anemia and oliguria, following a hemorrhagic shock. Many of the patients with IPRF have had what Brain *et al.* (1962) describe as a microangiopathic hemolytic anemia, characterized by fragmented red cells in the peripheral blood. Our patient did not have the peripheral blood examined for schistocytes, but a hemolytic anemia was present. There was no apparent transfusion reaction. The patient's sickle cell tests were negative.

The renal function never returned to normal requiring the patient today, a year later, to have hemodialysis 3 times a week. Hypertension developed late in the course but ran a malignant course until permanent hemodialysis was established. The observation of the prominent juxtaglomerular apparatus with abundance of renin crystals in the cells and the late developing hypertension favors a secondary activation of the renin-angiotensin system caused by the partial or complete occlusion of renal arterioles. Life is at the present time sustained by hemodialysis while the patient is waiting for a suitable kidney donor.

The light microscopic changes in the arteries and glomeruli were similar to what Robson *et al.* (1968) described in the first and second biopsies of their patient's number 1 (M.N.) and 2 (M.L.). The changes consisted of thickened glomerular basement membranes and vascular necrosis and thrombosis followed by obliteration of glomerular structures with vascular narrowing of the lumen due to intimal thickening.

Electron microscopy has only been performed in the early stage of IPRF where large subendothelial deposits have been described under the glomerular basement membrane. Sometimes these deposits had the characteristic periodicity of fibrin. Whereas, Robson *et al.* (1968) described different histologic changes by light microscopy in the patients where sequential biopsies were available, no such distinction was found in their electron microscopic description. While the thickening of the basement membrane with interposition of the mesangial cells and matrix in the peripheral tufts and the endothelial cell proliferation are non-specific and can be seen following other disease processes, the combination of these findings together with multiplication of basal lamina material between the mesangial and endothelial cells, appear to be unique.

Although fibrin or fibrin-like products were not identified in glomerular structures in this study, fibrinogen has been identified by immunofluorescent studies (Rosenmann *et al.*, 1969; Churg *et al.*, 1970) in both the glomerular basement membrane and in the arterial and arteriolar walls.

The finding in our patient of mesangial cells, containing abundant debris, surrounding the glomerular vascular lumen and the thickened, rarified basement membrane could be explained as being secondary changes to the resolution of the fibrin deposits seen in the early stages of IPRF.

Vassalli *et al.* (1963) studied glomerular changes with the electron microscope after rabbits had received injections of Liquoid (sodium polyanethol-sulfanate), thromboplastin or thrombin. These authors described similar morphologic changes that we have described in the early as well as the late stages of IPRF. It is

very tempting to suggest that activation of the coagulation system in IPRF is an important component of this disease. What triggers this activation is still uncertain. Many favor an adverse reaction to ergot preparations with resulting arteriolar spasm and thrombosis. Such a response must, however, be extremely rare since these drugs are widely used in obstetrics.

References

Brain, M. C., Dacie, J. V., Hourihane, D. O-B.: Microangiopathic haemolytic anaemia: The possible role of vascular lesions in pathogenesis. Brit. J. Haemat. 8, 358–374 (1962)

Clarkson, A. R., Meadows, R., Lawrence, J. R.: Post-partum renal failure. The generalized Schwartzman reaction. Aust. Ann. Med. **18**, 209–216 (1969)

Churg, J., Koffler, D., Paronetto, F., Rorat, E., Barnett, R. N.: Hemolytic uremic syndrome as a cause of postpartum renal failure. Amer. J. Obstet. Gynec. **108**, 253–261 (1970)

Donadio, J. V., Jr., Holley, K. E.: Postpartum acute renal failure: Recovery after heparin therapy. Amer. J. Obstet. Gynec. **118**, 510–516 (1974)

Eisinger, A. J.: The postpartum haemolytic uraemic syndrome. J. Obstet. Gynec. **79**, 139–143 (1972)

Epstein, F. H., Scully, R. E.: Renal failure two months postpartum. New Engl. J. Med. **288**, 93–99 (1973)

Finkelstein, F. O., Kashgarian, M., Hayslett, J. P.: Clinical spectrum of postpartum renal failure. Amer. J. Med. **57**, 649–654 (1974)

Larcan, A., Rauber, G., Laprevote, M. C., Lambert, H., Andre, J. L.: Le syndrome uremo-hemolytique du post-partum. Nouv. Presse méd. **3**, 1529–1534 (1974)

Lawrence, J. R., Meadows, R.: The relationship between postpartum renal failure and the hemolytic-uremic syndrome in glomerulonephritis. Morphology, natural history and treatment. Edit. by Kincaid-Smith, Mathew and Becker. New York-London-Syndey-Toronto: John Wiley and Sons 1973

Luke, R. G., Talbert, W., Siegel, R. R., Holland, N.: Heparin treatment for postpartum renal failure with microangiopathic haemolytic anaemia. Lancet **1970II**, 750–753

Ogg, C. S., Cameron, J. S.: Post-partum renal failure. Lancet **1969I**, 1317

Ponticelli, C., Imbasciatti, E., Tarantino, A., Graziani, G., Redaelli, B.: Post-partum renal failure with microangiopathic haemolytic anaemia. Nephron **9**, 27–41 (1972)

Robson, J. S., Martin, A. M., Ruckley, V. A., MacDonald, M. K.: Irreversible postpartum renal failure. Quart. J. Med. **37**, 423–435 (1968)

Rosenmann, E., Kanter, A., Bacani, R. A., Pirani, C. L., Pollak, V. E.: Fatal late postpartum intravascular coagulation with acute renal failure. Amer. J. med. Ass. **257**, 259–273 (1969)

Scheer, R. L., Jones, D. B.: Malignant nephrosclerosis in women post partum. J. Amer. med. Ass. **201**, 106–110 (1967)

Vasalli, P., Simon, G., Rouiller, C.: Electron microscopic study of glomerular lesions resulting from intravascular fibrin formation. Amer. J. Path. **43**, 579–617 (1963)

Wagoner, R. D., Holley, K. E., Johnson, W. J.: Accelerated nephrosclerosis and postpartum acute renal failure in normotensive patients. Ann. intern. Med. **69**, 237–248 (1968)

P. H. B. Carstens, M.D.
Department of Pathology
University of Louisville School of Medicine
Louisville, Kentucky 40201, USA