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New Clinical and Ultrastructural Aspects in Leptospirosis icterohaemorrhagica (Weil's Disease)

A Clinical, Light- and Electron Microscopic Study*

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Summary. Clinically, the coincidence of jaundice and acute renal failure with elevation of serum bilirubin, transaminases and fibrinogen, as well as thrombocytopenia and normal prothrombin time are characteristic for Morbus Weil. Liver biopsy, 13 days after onset of the disease, showed scattered foci of liver cell necrosis with surrounding leucocytic infiltration and mesenchymal proliferation as well as intrahepatic cholostasis. Kidney biopsy 17 days after the onset of the disease showed an acute interstitial inflammatory edema, and electronmicroscopically, a glomerulonephrosis with a loose, finely granular thickening of the lamina rara interna. The latter lesion is not completely restituted after $4^1/_2$ months. Glomerular and intertubular endothelial cells show severe reparatory-proliferative alterations after $2^1/_2$ weeks. The glomerulonephrosis as well as the interstitial edema are considered as consequence of the direct lesion of endothelial cells by leptospirae, the anuria is considered as consequence of the interstitial edema as well as of the circulatory collapse.

Zusammenfassung. Klinisch ist das Zusammentreffen von Ikterus und akuter Niereninsuffizienz mit Erhöhung von Serumbilirubin, Transaminasen und Fibrinogen, sowie Thrombocytopenie und normaler Prothrombinzeit charakteristisch für Morbus Weil. Die Leberbiopsie am 13. Tag zeigt spärliche Herde mit Leberzellnekrose, umgeben von Leukocyteninfilatration und mesenchymaler Proliferation, daneben intrahepatische Cholostase. Die Nierenbiopsie am 17. Tag ergibt ein akutes interstitielles entzündliches Ödem und elektronenmikroskopisch eine Glomerulonephrose mit lockerer, feingranulärer Verdickung der Lamina rara interna. Letztere Veränderung ist nach $4^1/_2$ Monaten noch nicht völlig restituiert. Glomeruläres und intertubuläres Endothel lassen nach $2^1/_2$ Wochen schwere, reparatorisch-proliferative Veränderungen erkennen. Die Glomerulonephrose und das interstitielle Ödem werden als eine Folge der direkten Endothelläsion durch die Leptospiren, die Anurie als Folge des interstitiellen Ödems und des Kreislaufkollapses aufgefaßt.

Clinical symptoms and evolution of leptospirosis icterohemorrhagica have been described in detail by several authors (Edwards, Gsell, Heath, McCrumb, Weil). Since neither the patients' complaints nor his examination may reveal pathognomonic findings, diagnosis is difficult until serologic results are both positive and available, i.e. only during the third week after onset of the disease, at a time when the most critical period is already over. The clinical part of this study shows a practical way to this diagnosis by means of some simple laboratory tests.

The kidney involvement in Weil's disease is an interesting example of a special form of renal insufficiency. Furthermore, glomerular lesions can be demonstrated

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by electron microscopy which may help to understand other glomerular alterations. Finally, this is, as far as we know, the first report on biopsy findings three weeks and 19 weeks after the onset of Weil's disease.

Methods

Formalin fixed material for light microscopy was paraffin enbedded. Staining: HE, CAB, Berlin-blue, PAS, Methenamin-silver.—For electron microscopy (EM) fixation in glutaraldehyd. Secondary fixation in osmium, Epon-embedding, staining by uranyl-nitrate and lead-acetate.

Observations

Case History. (See Fig. 1); 42-year-old mason was admitted to the Renal Unit of our Medical Department with myalgia in the legs, diarrhea, repeated vomiting, fever of 37.4° C and jaundice. He complained of headache and told us that he had been working on old canalisation tubes for the last two weeks.

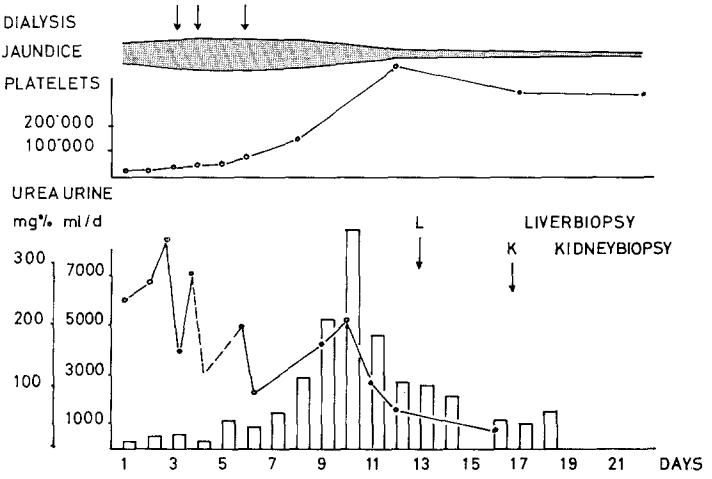
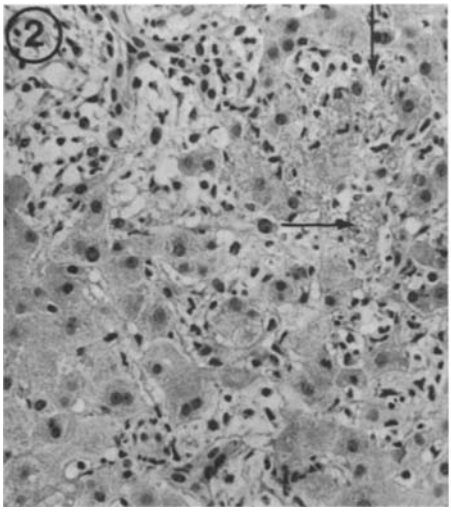


Fig. 1. Clinical course of our case

On admission the conscious patient presented conjunctivitis and bleeding from his nose. Both hands were covered by multiple skin lesions. Blood pressure was 110/70 mm Hg. Laboratory examinations: SR 116/120 mm, hemoglobin 13.2 g%, WBC 9 300, platelets 27000; proteinuria and significant hematuria. Bloodchemistry: sodium 137 mEq/l, potassium 4.0, 4.0 mEq/l, urea 240 mg%, creatinine 10.2 mg%, Quickvalue 100%, fibrinogen 1480 mg%, bilirubin 9.5 mg% with a direct fraction of 66%, SGOT 33.5 mU/ml, SGPT 19 mU/ml, alcaline phosphatase 42 mU/ml, amylase 96 SU, glucose 113 mg%.

Two days after admission, oliguria of 300 and 500 ml/24 hrs was noted, the patient's general condition deteriorated, pericarditis developed and, in the early morning of the third day, a cerebral attack occured. A Scribnershunt was inserted (Dr. H. Burri, Dept. of Surgery, Lucerne) in the patient's right arm, and the patient was dialysed with a travenol RSP coil-dialyser for 5 hrs. Because of pericarditis and the low platelet count with bleeding tendency this was done in regional heparinisation. Blood-urea decreased from 340 to 160 mg/% (Fig. 1). Since oliguria persisted and blood-urea increased rapidly after dialysis, this procedure was repeated three times, until polyuria started on the seventh day after admission. The platelets also increased, serumbilirubin decreased and the patient's general condition improved.



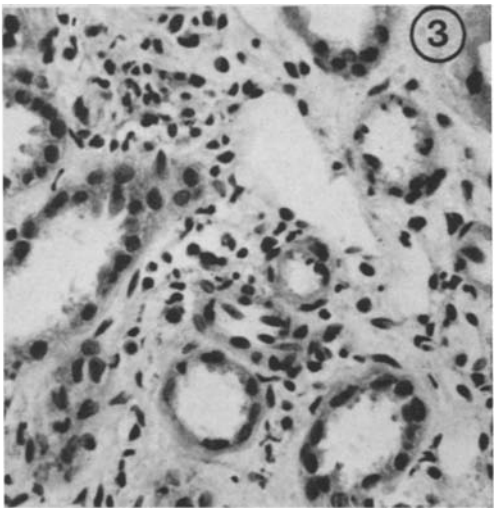


Fig. 2. Liver biopsy: small foci of mesenchymal cells, leucocytes and necrobiosis of liver cells (→). H.E., ×250

Fig. 3. 1st kidney biopsy: subacute exsudativ interstitial nephritis. Tubular cells flattened. H.E. ×340

Leptospirosis agglutination titers:

	7	9	21	23	31	37 days[a]
L. australis	neg.	neg.	1:100	neg.	neg.	neg.
L. canicola	neg.	1:100	1:200	1:100	neg.	neg.
L. icterohem.	neg.	neg.	1:200	1:400	1:800	1:800

[a] Days after onset of the disease.

The increase of the platelet count and the missing need for further hemodialysis treatments enabled us to do a liver biopsy on the 13th, and a kidney biopsy on the 17th day after admission.

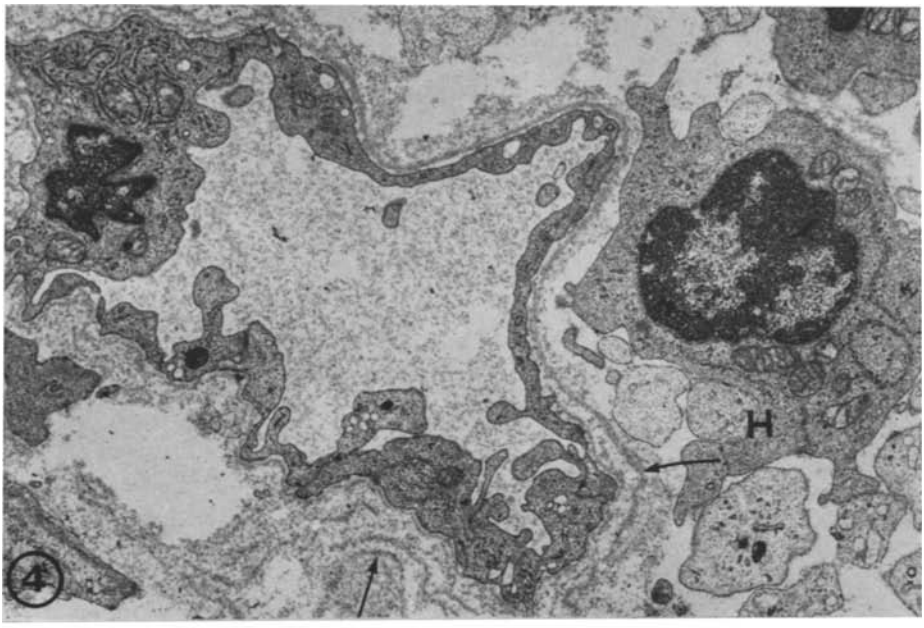
Liver biopsy. Sparse infiltrates of neutrophil leucocytes and mesenchymal cells, particularly in the region of the Glisson's capsules (Fig. 2). Adjacent liver cells with eosinophilic granular cytoplasm and pyknotic nucleus. Here and there ballooned cells with many bile droplets. Collagen fibres in the area of the infiltrates slightly increased, lobules in good condition, with ubiquitously scattered bile thrombi and sparse histiocytes loaded with bile.

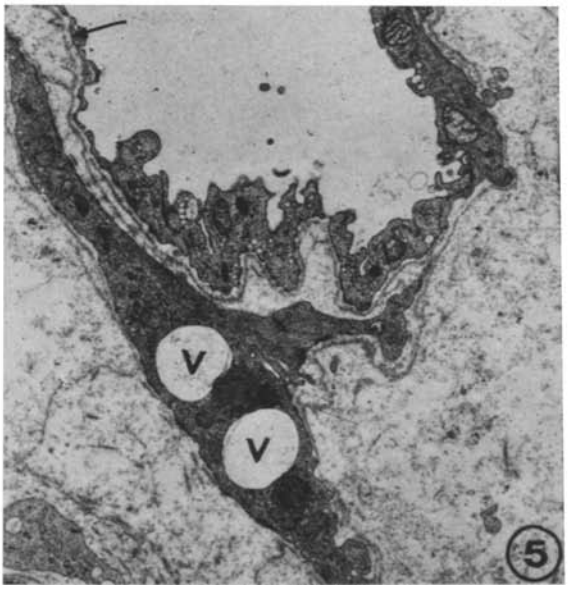
Diagnosis: Healing parenchymatous hepatitis.

1st Kidney Biopsy

Light microscopically, the typical picture of a non-destructive interstitial nephritis with flattening of the proximal tubular epithelium and pyknosis of the nuclei was seen (Fig. 3). Interstitial tissue with focal edema and some inflammatory foci consisting mainly of lymphocytes and a few histiocytes. Intertubular capillaries dilated, glomerula as well as vessels unchanged, also in semi-thin Epon sections.

EM: Severe edema of the interstitial tissue with inflammatory cells: partly similar to the immunoblasts of kidney transplants, partly highly activated histiocytes with polymorphic





Figs. 4 and 5. 1st kidney biopsy: intertubular capillary with swollen, activated and vacuolated endothelium. Basal membrane edematous and split (→). *H* Histiocyte; *V* Vacuoles in swollen pericyte. EM, Fig. 4: ×5540; Fig. 5: ×9950

branches (Fig. 4), numerous small and large lymphocytes, scattered plasma-cells. Proliferation and high-grade activation of the endothelial cells of the intertubular capillaries is striking (Fig. 4). The basal membrane is completely coated by the cytoplasmic layer without any intervals, large mitochondria, ergastoplasm distinct. Basal membrane frequently split,

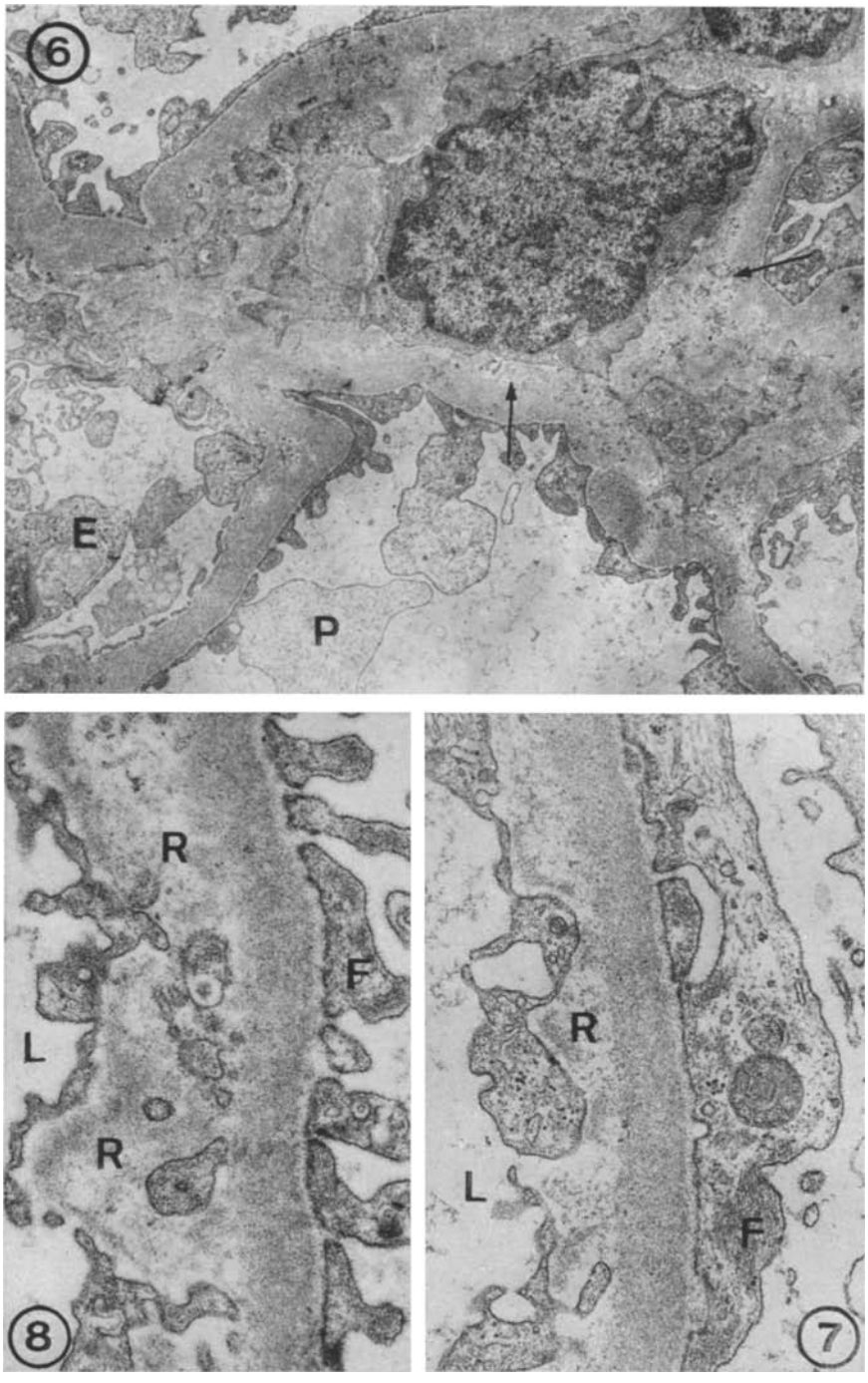
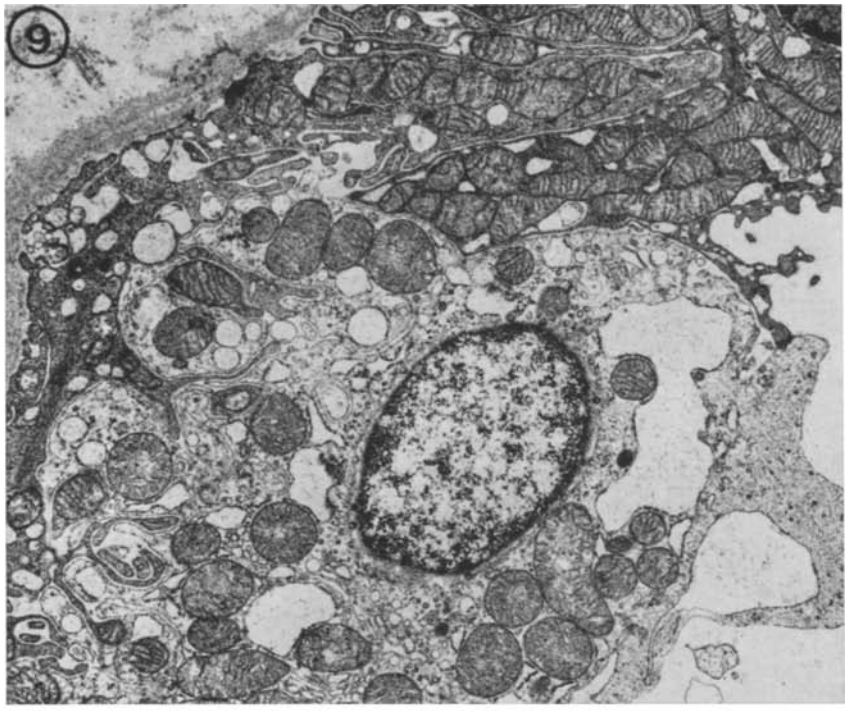


Fig. 6. 1st kidney biopsy: Lamina rara interna of basal membrane along mesangial cell thickened and spongy (→). *P* swollen protrusion of pericyte; *E* proliferation and arcade formation of endothelial cell. EM, ×6900

Figs. 7 and 8. 1st kidney biopsy: periphery of glomerular loop. Lamina rara interna (*R*) irregularly thickened and finely granular with inclusion of endothelial cell parts. *F* fusion of foot processes. Proliferation of endothelial cells. *L* capillarly lumen EM, ×21200



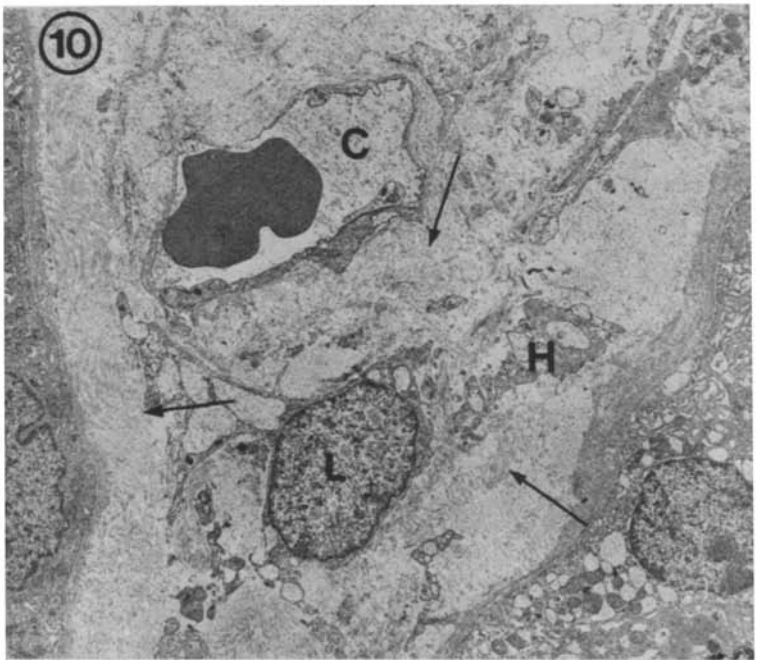


Fig. 9. 1st kidney biopsy: cell of proximal convoluted tubule. Vacuoles of different size, swelling of mitochondria. Cytoplasmic edema. EM, ×6200

Fig. 10. 2nd kidney biopsy: intertubular capillary (*C*) with normal endothelium. *H* process of histiocytes. Increased collagen formation (→). *L* small lymphocytes. EM, ×3570

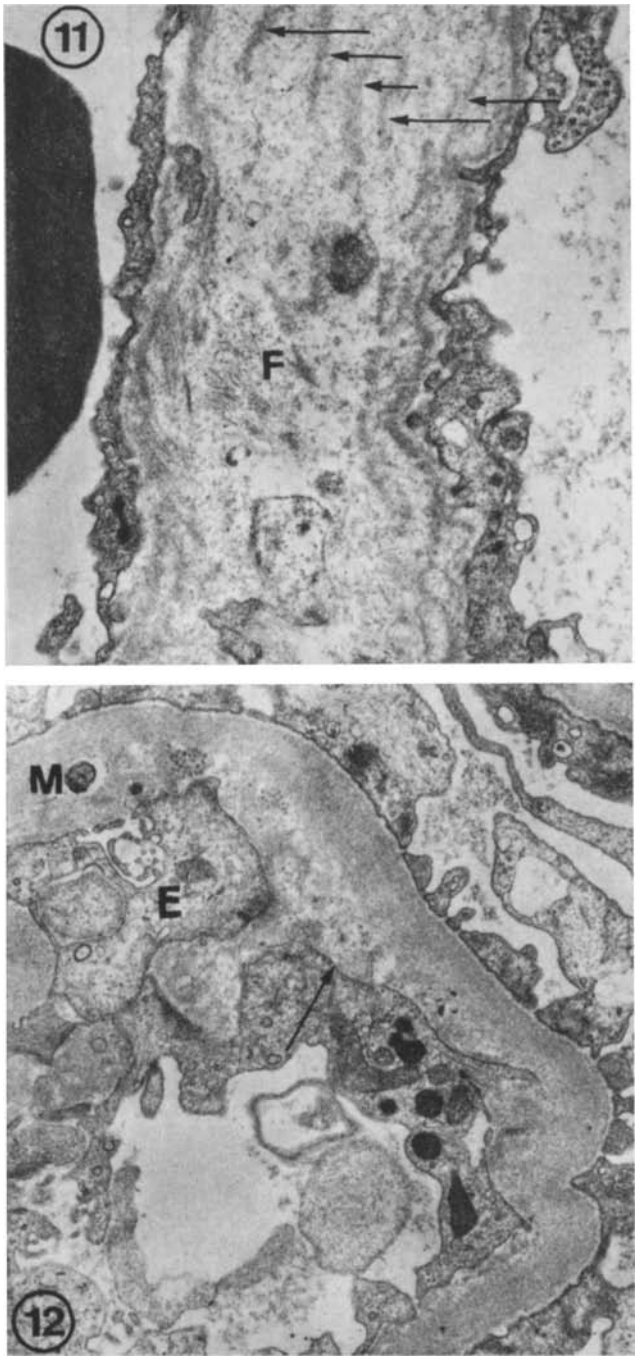


Fig. 11. 2nd kidney biopsy: wall between two intertubular capillaries, shows split basal membrane (→) and fibrin formation (*F*). Endothelium with slight proliferation. EM, ×12500

Fig. 12. 2nd kidney biopsy: periphery of glomerular loop. Lamina rara interna in a few foci, still thickened and granular (→) with inclusion of myelin body (*M*). Endothelial proliferation (*E*) still very distinctive, dark bodies = phagolysosomes EM, ×12100

between the layers severe edema (Fig. 4), capillary pericytes activated, with large vacuoles (Fig. 5). Tubular basal membrane intact, epithelium, mainly of the proximal tubules, with few pyknotic nuclei, swelling of the mitochondria and intense vacuolation (Fig. 9). Focally, numerous cytophagosomes (hyaline droplets) in the cytoplasm.

In the glomerula, no distinct inflammatory alterations to be seen (Fig. 6), pericytes highly activated, with villous processes. Fusion of foot processes merely here and there (Fig. 7). The peripheral basal membrane shows subendothelially in numerous loops irregular, fine-grained thickenings of the lamina rata interna (Figs. 7 and 8). In these, constituents of cytoplasm are not infrequently enclosed (Fig. 8). The same alteration is found in the basal membrane along the mesangium (Fig. 6). The mesangium itself not significantly enlarged, the cells not activated (Fig. 6). The endothelium of the loops (Figs. 6, 7 and 8) changed analogous to that of the intertubular vessels, plenty of ribosomes and partly large mitochondria recognizable, frequently garland-like protuberances reaching into the lumen (Fig. 6). Capsular epithelium and its basal membrane unchanged.

One month after the onset of the disease, the patient was dismissed in good general condition. Slight pretibial edema persisted for a few days.

$4^1/_2$ months later, the patient was readmitted for a second kidney biopsy. At this check-up, hemoglobin, WBC, thrombocyte count, sedimentation rate, serumbilirubin, transaminases and Quickvalue were all within normal limits. The creatinin clearance was 138 ml/min

2nd Kidney Biopsy

Light microscopically, merely scattered peritubular foci of fibrosis, not compact, with sparse infiltrates of lymphocytes.— EM: still slight edema of the interstice as well as distinct foci of fibrosis (Fig. 10). In the latter, distinct production of collagen, scattered lymphocytes and processes of the histiocytes. The endothelium of the intertubular capillaries still shows some proliferation (Fig. 11). Basal membrane merely split up here and there, with production of fine fibrilles between the layers (Fig. 11). Tubuli completely normalized. In the peripheral loops of the glomerula only very few foci with disaggregation of the lamina rara interna, and partly distinct focal activation and proliferation of the endothelium (Fig. 12).

Comments

In the presence of renal failure and jaundice, leptospirosis icterohemorrhagica has to be considered as a diagnosis. History with regard to the patient's profession, pain in the lower limbs, headache, fever, conjunctivitis and epistaxis might suggest Weil's disease, however, none of these features is pathognomic. Agglutination titer becomes positive only when the most critical phase has passed. Therefore other laboratory examinations indicating Leptospirosis Weil with the utmost probability, are of special interest.

There is indeed a typical laboratory pattern consisting of hyerbilirubinemia, slightly elevated transaminases, normal Quickvalue, hyperfibrinogenemia and thrombocytopenia concomitant with renal failure, as demonstrated in 5 cases summarized in Table 1.

In previous reports (Gsell, 1952; Edwards, 1959) the significance of the liver lesion has been stressed because of the often intensive hyperbilirubinemia; later the discrepancy between jaundice and slightly elevated transaminases as well as mild hepatocellular damage became evident in liver biopsy specimens (Cohn, 1961; Kalk, 1965; Schmidt, 1970). The early liver biopsy in our patient (B.H.) confirms this fact.

We previously proposed to use blood clotting factors II, V, VII and the Quickvalue as a parameter of livercell damage (Colombi, 1970). The turnover of these proteins, mainly products of the liver cells, is short enough to give actual informa-

tion on protein synthesis capacity of these cells. In our patients with leptospirosis icterohemorrhagica the normal Quick-value is equivalent to mild hepatocellular damage found in the liver biopsy specimen. The conformity is specially remarkable since in the acute phase thrombocytopenia is a contraindication for liver biopsy.

Table 1. *Clinical and laboratory data in 5*

Name	Age	Sex	Profession	Aggl. Titer		
				1st	2nd	3rd
B.P.	31	♂	bucher	neg.	1:800	?
S.A.	19	♂	chemist	neg.	1:800	1:1900
V.W.	39	♂	chemist	neg.	1:100	1: 800
B.H.	41	♂	mason	neg.	neg.	1: 800
H.E.	28	♂	cook	neg.	neg.	1:1600

Besides the normal values of the Quick and the clotting factors II, V and VII there is a regular increase in fibrinogen as previously recorded by Grazioli *et al.* (1968). Considering the lack of morphological alterations it seems therefore rather probable, as suggested by Schmidt *et al.* (1970), that hyperbilirubinemia in Weil's disease is an acquired enzymatic defect.

In contrast to these mild hepatic damages, renal involvement is of major importance. Renal insufficiency and thrombocytopenic bleeding are the main cause of death in this entity (Schmidt, 1970). Therefore, dialysis is a lifesaving procedure in oliguric, uremic patients with leptospirosis Weil. Schmidt's patient did not survive in spite of peritoneal dialysis, and in one of our patients (Fig. 13) peritoneal dialysis was not efficient enough to prevent serumurea increase. This was certainly due to the patient's catabolism. In this case, after 5 days of peritoneal dialysis, we were forced to take the patient in a coil-hemodialysis. This treatment, as previously recommended by Kaeding *et al.* (1963) and Valek *et al.* (1959) was successful.

The main morphological alteration of the kidney lies undoubtedly in the inflammatory edema of the interstice (Rippmann, 1954; Zollinger, 1966; Sitprija and Evans, 1970) leading to a large increase of weight of such kidneys (Kaneko, 1922; Stiles *et al.*, 1946; Rippman, 1954). The same alteration was also observed in the analogous disease of dogs (Mc Intyre and Montgomery, 1952; Freudiger, 1952), and in rats with leptospirosis (De Martino *et al.*, 1969). The maximum of this alteration seems to appear on approximately the 7th to 8th day of the disease. In our observation, a severe edema still exists after 3 weeks. The second biopsy reveals this edema to turn into a proliferation of the connective tissue (in dogs: McIntyre and Montgomery, 1952). The acute interstitial non-destructive nephritis of the chromoprotein kidney too can lead to such a sclerosis of the interstice (Zollinger, 1966).

The maximum of the inflammatory infiltrates is observed on the 10th to 14th day (Beitzke, 1921; Austoni and Cora, 1961). Apart from the elements interpreted as immunoblasts, we found relatively many activated histiocytes and

numerous lymphocytes of various size. The picture does not differ from that of the usual non-destructive interstitial nephritis (Zollinger, 1966).

The alterations of the intertubular vessels observed by us have apparently not been described until now. After 3 weeks they consist of severe swelling and ac-

patients with Weil's disease (predialysis values)

Blood-urea (mg %)	Thrombo-cytes per cumm	Quick value (%)	Fibri-nogen (mg %)	Bili-rubin (mg %)	SGOT WU	SGPT WU
420	43000	85	887	18.6	63	32
325	—	75	?	1.8	71	45
415	31000	85	556	24.0	50	69
340	27000	100	1480	13.8	34	12
300	12000	88	520	21.3	54	26

tivation of the endothelium as well as proliferative alterations which we interpret as being regenerative, and which can last up to $4^1/_2$ months. The disaggregation and splitting-up of the capillary basal membrane suggest an increase of permeability of the capillary. The same is true for the vacuolation of the histiocytes and in the pericytes of the small vessels. The alteration seems to be largely reversible apart from small scattered split-up foci of the basal membrane.

Long has it been known that there is a significant tubular damage which, light microscopically, is within modest limits, however (Sitprija and Evans, 1970). The enzymatic activity of the tubular cells is said to decrease rapidly (DeBrito *et al.*, 1966/1967). While we could find no significant damage of the tubular basal membrane, it is, according to Schmidt *et al.* (1970) and Arean (1962), said to be focally destroyed.—We could nowhere show leptospirae, as we presumably examined too late. DeMartino *et al.* (1969) showed in rats that plenty of leptospirae are in the tubular cells, in the interstice and also in the endothelium.

Light microscopically, the glomerula were unchanged as noted by the other authors as well. Only Griffin *et al.* (1951) described histologically thickening of the loops and proliferation of the cells. Electron microscopically, a focal thickening of the lamina rara interna is mainly found, partly nodularly, with enclosures of cytoplasm (Sitprija and Evans, 1970; DeBrito *et al.*, 1965/1967). The fusion of the foot processes of the podocytes is within modest limits and may be interpreted as secondary change. The severe proliferative alterations of the endothelium with cell activation are morphologically largely equivalent to those of the intertubular capillaries. On the whole, the observed glomerular alterations explain the early appearance of proteinuria in Weil's disease (Schmidt *et al.*, 1970).

The glomerular alteration in itself seems to be reversible (see also Sitprija and Evans, 1970). Our 2nd biopsy after $4^1/_2$ months shows, however, that the process regresses extraordinaryly slowly due to the slow rate of turn-over of the basal membrane.

The question arises how to interpret this glomerular alteration. Reubi (1968) lists Weil's disease under glomerulonephritis though he did not find inflamma-

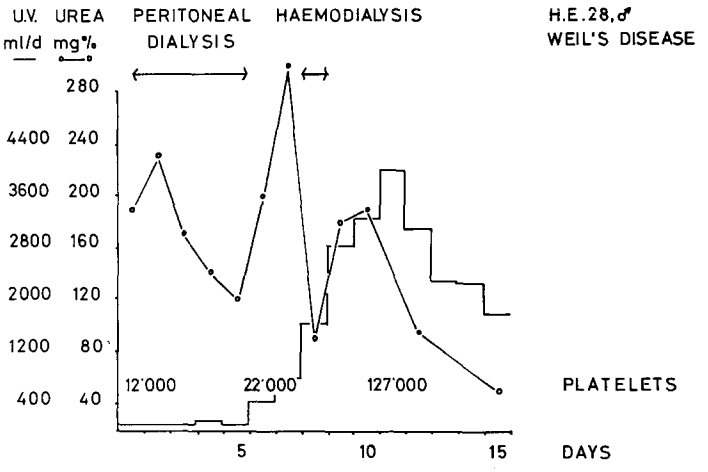


Fig. 13. Clinical course of a case of leptospirosis icterohaemorrhagica. Effect of peritoneal and haemodialysis. Clinical course of a 28-years-old patient with Weil's disease. Urine volume, bloodurea, and platelet count during the first 15 days after admission to hospital. The periods of peritoneal dialysis and haemodialysis are indicated by ←→

tory alterations in 2 of his own cases. The description of an acute glomerulitis is not convincing either (Stiprija and Evans, 1970). Principally, it is possible that the subendothelial deposits are equivalent to immune deposits (Masugi type), proving immunofluorescent examinations lack however. The fact that this alteration existed $4^1/_2$ months after the onset of the disease, speaks against immune bodies in this case. An actual proliferation of the cells in the region of the glomerula is lacking. We therefore reject the existence of a glomerulitis.

The existence of a hepatic glomerulonephrosis is probably to be negated, for the deposits in the latter mentioned type are not scattered, fine-grained, but electron dense and much more osmiophilic; also, they never observed in acute diseases of the liver. Thus a direct damage of the endothelium with secondary disturbance of the permeability of the capillary wall and subendothelial deposit of plasma proteins conditioned by it, remains to be assumed. Strongly indicating in this direction is the fact that principally very similar alterations were found by us in the peritubular vessels. Since leptospirae could be shown in animal experiences (DeMartino *et al.*, 1969) as well in the endothelial as in the epithelial cells, and free in the interstice, the assumption of a direct damage of the endothelial cells by leptospirae is reasonable. We see a further argument in the fact that the glomerolopathy following renal transplants shows a rather analogous picture, and that the intertubular capillaries are similarly damaged. In most authors's opinions, the endothelium of transplants seems to be the target butt, thus the antigen, of the immune cells. Thus, in both cases there is a primary damage of the endothelium, in the case of Weil's disease by direct effect of the leptospirae, less probable by circulating toxins (DeBrito *et al.*, 1967).

A final question concerns the frequent appearance of anuria in Weil's disease. Some authors assume the primary disturbance of the fluid balance to be an effect of a toxin causing circulatory collapse (Schmidt *et al.*, 1970; Austoni and Cora,

1961; Sitprija, 1968; Reubi, 1968). Sitprija (1968) explains this by the fact that an insufficiency of the kidneys can exist without an interstitial nephritis, a statement we cannot confirm, however. According to Austoni and Cora (1961), the circulatory collapse leads to a capillary disturbance of permeability, thus to a renal ischemia. We believe to have shown that this disturbance of permeability, ordinarily restricted to the kidneys, is caused by a direct effect of the leptospirae. Other authors assumed a combined effect of the circulatory collapse and tubular necroses (Schmidt *et al.*, 1970) and a mere consequence of the tubular necrosis resp. (Arean, 1952). Considering our observation at issue as well as numerous cases examined light optically (Zollinger, 1966), the assumption of a combined effect of serous interstitial nondestructive nephritis on one hand, and circulatory collapse on the other, seems to lead to acute kidney insufficiency.

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