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Study of Haemostasis in Nephropathies Associated with Pulmonary Haemorrhage

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Three cases of pulmonary haemorrhage associated with various forms of nephropathy have been studied, and 15 laboratory tests have been carried out to analyse the observed coagulation defects. Also three kinds of capillary tests have been performed.

Case 1. Goodpasture's syndrome. Laboratory tests pointed to hypercoagulability. Anomalies characteristic of consumption coagulopathy were observed in the terminal phase. Bleeding tendency appeared to be due to capillary damage.

Case 2. Lupus nephropathy. Haemorrhage of the lungs, brain, skin and eyeground was caused by thrombocytopenia.

Case 3. Malignant nephrosclerosis. The disease was marked by hyperfibrinogenaemia and diminished prothrombin consumption. Disturbance of thromboplastin production may have been a pathogenetic factor of the bleeding tendency.

Although at least one capillary test was positive in all three cases, the coagulation studies made it probable that the pathomechanism of pulmonary haemorrhage is not the same in all nephropathies.

Introduction

Pulmonary haemorrhage may occur in various nephropathies if the patient develops uraemic pneumonitis in the terminal phase [23, 51]. Acute glomerulonephritis in children may be accompanied by pulmonary lesions which sometimes induce haemoptysis [22]. In certain cases of periarteritis nodosa [32, 40, 49], systemic lupus erythematosus [2, 37, 42], Wegener's granulomatosis [26] and Schönlein—Henoch purpura [39, 63], the combination of nephropathy and pulmonary haemorrhage is due to that both the lungs and the kidney are affected by the primary disease. In most cases of Goodpasture's syndrome pulmonary haemorrhage precedes the appearance of renal symptoms. This rare disease, generally regarded nowadays as a nosological entity [4, 10, 41, 46], is a syndrome combining haemorrhagic alveolitis with proliferative glomerulonephritis. So far, three such cases have been reported from Hungary [9, 16, 59].

Material and method

We have observed three cases of nephropathy combined with pulmonary haemorrhage. Bleeding tendency was studied by the following methods and by the determination of the following parameters.

1. Determination of capillary fragility by the positive-pressure methods of Rumpel-Leede and Göthlin, and by the negative-pressure method of Borbély.
2. Bleeding time according to Duke.
3. Whole blood clotting time according to Lee and White.
4. Clot retraction according to Biggs and McFarlane.
5. Coagulation time of recalcified plasma according to Howell.
6. One-stage prothrombin time according to Quick.
7. Study of serum-coagulation accelerating factor according to Horn, Kovács and Altmann.
8. Prothrombin consumption.
9. Thrombin time.
10. Thrombin clotting time in the presence of toluidine blue.
11. Thrombin inactivation time according to Gerendás.
12. Platelet count by phase contrast microscopy according to Brecher and Cronkite.
13. Fibrinogen gravimetry.
14. Determination of fibrinogen B (labile fibrinogen) according to Lyons.
15. Euglobulin lysis time according to von Kaulla and Schultz.
16. Thromboelastography according to Hartert.

The results of the coagulation tests are represented according to Gerendás. Normal thromboelastogram (TEG) is indicated by a broken line; the hatched area in Fig. 3 corresponds to the scatter of the normal fibrinogen values. The level of serum complement was determined by the method of Lange (with 1.0 U as the lowest normal value).

All patients were subjected to ophthalmoscopy, and the Addis count of erythrocytes was daily performed. Pulmonary alterations were radiographed.

Case records

Case 1. E. S., female, 19, was hospitalized in our Department from February 27 to March 25, 1969.

The patient had developed acute catarrhal rhinitis two months before admission, began to cough and expectorate sputum containing fresh blood. She felt stabbing pain on respiration and developed haematuria. A provincial hospital diagnosed Goodpasture's syndrome. She was then referred to us on account of grave anaemia and initial uraemia.

On examination: grave dyspnoea, cough, pulmonary haemorrhage, debility. Blood pressure, 110/70 mm Hg. No signs of pathology on the eyeground. Roentgenogram shows confluent focal lesions with indistinct boundaries in both lower lobes (Fig. 1).

Laboratory: ASO, 100 units; red count, 1 900 000; haemoglobin, 5.38 g/100 ml; haematocrit reading, 14%. Direct and indirect Coombs test negative. Urine: acid pH; spontaneous specific gravity, 1008 to 1013; protein excretion 3.2 g/24 hrs.

Addis counts: erythrocytes, 200 000 000; leucocytes, 2 000 000; cats, 300 000. Bacteriological examination negative; ESR 165 mm in 1 hour; total serum protein 5.13 g/100 ml. Paper electrophoresis: albumin, 51%; alpha 1, 3.6%; alpha 2,

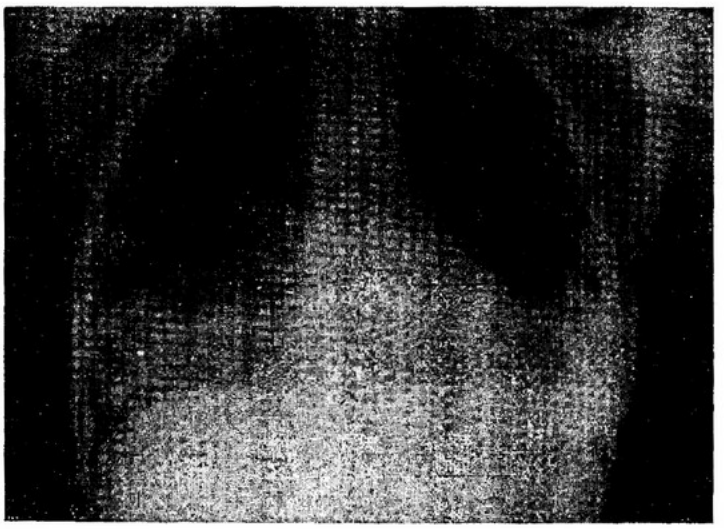


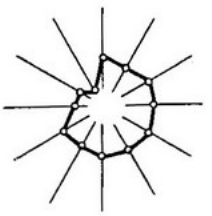
Fig. 1. E. S., female, 19. Goodpasture's syndrome. Confluent focal lesions with indistinct boundaries in both lower lobes

Capillary tests:

Rumpel-Leede	positive
Göthlin	negative
Borbély	20 Hgcm

Coagulogram:

Bleeding time	170″
Clotting time	3′ 50″
Retraction	normal
Recalcification	170″
Prothrombin time	14″ 100%
Serum effect	26%.
Prothrombin consumption	44″
Thrombin time	23″
Toluidine blue time	15″
Thrombin inactivation	0.22 dm
Thrombocyte count	190 000
Fibrinogen	630 mg%
Fibrinogen B	+++
Euglobulin lysis time	72 hrs



TEG

r 6′
k 2′45″
mε 488

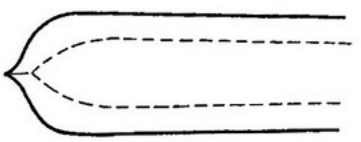


Fig. 2. E. S. Coagulation studies point to hypercoagulability. The coagulogram is represented according to Gerendás. The normal TEG is indicated by broken line

19%; beta, 20.3%; gamma, 16.1%. NPN, 93 mg/100 ml; serum creatinine, 2.07 mg/100 ml; endogenous creatinine clearance, 15 ml/min; serum cholesterol, 159 mg/100 ml.

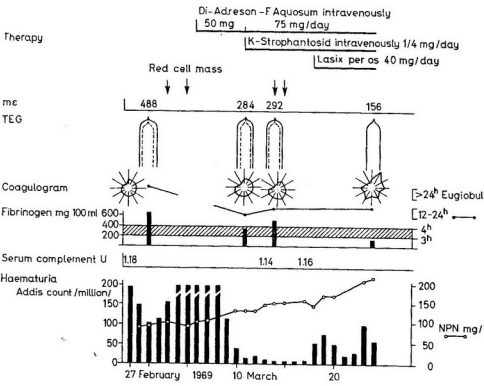


Fig. 3. E. S. The diagram shows the manner of treatment, the values regarding coagulation, serum complement, haematuria and NPN

Data regarding capillary tests, coagulography and TEG are shown in Fig. 2. The Rumpel-Leede test was positive, the value of capillary resistance (determined according to Borbély) amounted to 20 cm Hg. A striking increase in the amount of plasma fibrinogen was registered. Determination of the euglobulin lysis time revealed no fibrinolysis: the euglobulin clot was still undissolved after 48 hours. The TEG values pointed to a pronounced increase of coagulability.

Fig. 3 shows the more important results of our repeated examinations together with the quantitative data of haematuria and the NPN values. Descending from the initial high level, fibrinogen eventually dropped below the normal value. The maximum elasticity of thrombus (mε), too, diminished but still indicated hypercoagulability at the last examination. There was no essential change in the markedly protracted euglobulin lysis time. In the terminal phase the coagulation time of recalcified plasma and the thrombin time became longer, the rate of thrombin inactivation was accelerated, while the coagulation accelerating effect of the serum became weaker.

Since the patient's condition deteriorated we decided to start haemodialysis which, however, could not be realized as the patient died on the next day.

Diagnosis: Goodpasture's syndrome.

Post mortem: Total weight of kidneys, 250 g; cortex indistinct. All glomeruli were markedly diseased but their lesions dated from different points of time: while many glomeruli displayed signs of fresh necrotizing segmental glomerulitis, the majority showed complete fibrotic-hyaline transformation, and their contours had become mostly blurred. The distended tubules were coated with atrophied

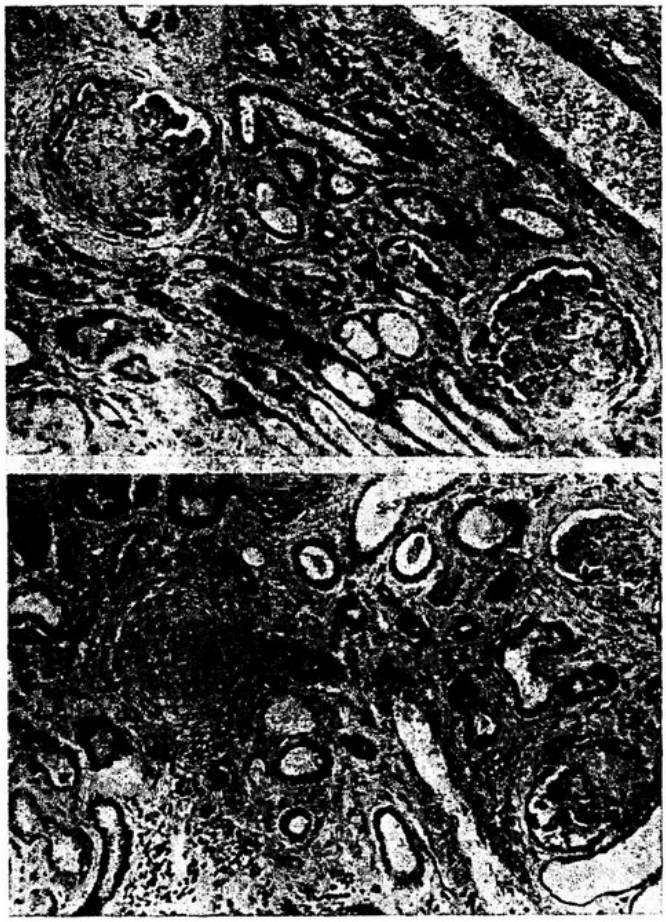


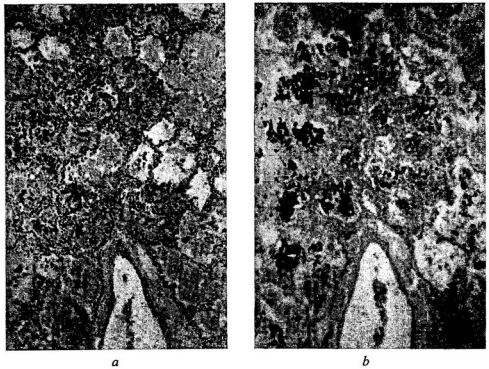
Fig. 4. E. S. Above: necrotic segmental glomerulitis. Below: a completely fibrotic and hyaline glomerulus. Tubular dilatation. Haematoxylin-eosin, ×160

epithelium (Fig. 4). There were haemorrhagic patches in all lobes of the lungs; their sections showed fresh bleeding and haemosiderosis. A moderate amount of fibrin was found in the alveoli (Fig. 5).

Case 2. J. K., female, 23, was treated and cared for by us for 7 years. She received in 1961 a prolonged steroid treatment on account of idiopathic nephrotic syndrome with the result that – except for proteinuria – the renal symptoms had subsided. The patient developed in 1965 metrorrhagia, then massive haemoptysis, later gross haematuria, extensive haemorrhage of the eyeground,

ecchymosis and cerebral haemorrhage which gave rise to transitory hemiplegia. The thoracic roentgenogram revealed extensive bilateral nodular lesions (Fig. 6).

We established thrombocytopenic coagulopathy as the cause of the patient's bleeding tendency (Fig. 7).



a *b*

Fig. 5. E. S. Lung. *a*: Staining with haematoxylin-eosin shows fresh blood and a moderate amount of fibrin in the alveoli. *b*: Iron reaction reveals intensively reacting macrophages filling the alveoli. ×100

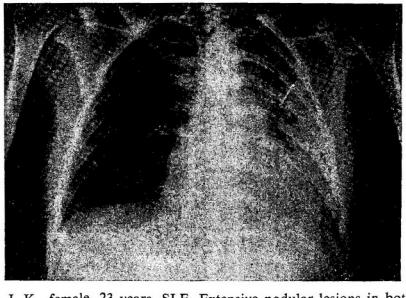


Fig. 6. J. K., female, 23 years. SLE. Extensive nodular lesions in both lungs

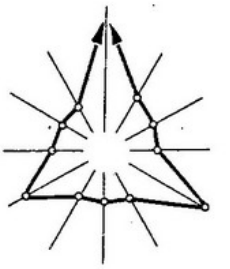
As a result of massive steroid treatment and substitution therapy, the bleeding tendency subsided after 3 months, while another 3 months had elapsed before the laboratory findings became normal. The patient developed epilepsy in 1966 and arthralgia in the spring of 1967. It was at that time that we succeeded in demonstrating the presence of L. E. cells in the patient's blood which confirmed our hitherto tentative diagnosis of systemic lupus erythematosus. The dosage of prednisolone had to be reduced on account of steroid ulcer. This measure led to a renewal of the thrombocytopenic bleeding, and the patient was then lost amidst the signs of brain pressure.

Capillary tests:

Rumpel-Leede	positive
Göthlin	positive
Borbély	<10 Hgcm

Coagulogram:

Bleeding time	12′
Clotting time	3′ 30″
Retraction	∅
Recalcification	280″
Prothrombin time	14″ 100%
Serum effect	21%
Prothrombin consumption	13″
Thrombin time	25″
Toluidine blue time	19″
Thrombin inactivation	0.35 dm
Thrombocyte count	20 000
Fibrinogen	340 mg%
Fibrinogen B	—
Euglobulin lysis time	180′



TEG

r 5′
k not measurable
mε 11

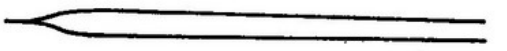


Fig. 7. J. K. Serious thrombocytopenic coagulopathy

Post-mortem: the lungs showed several earlier haemorrhages, while the test for iron remained negative, and even histological examination failed to demonstrate deposits of haemosiderin. The kidneys presented the picture of treated lupus nephritis. Death was due to subdural haematoma. As an accidental finding, autopsy revealed a two-month pregnancy which had presumably contributed to the exacerbation of SLE.

Case 3. I. T., male, 36, was hospitalized in our Department from February 27 to March 18, 1969 with uraemia, cardiac failure and periodic haemoptysis. Blood pressure, 260/160 mm Hg. Eyeground: narrow arteries with rigid walls and Gunn's crossing sign. Scattered exudative foci over the retina with past and pre-

sent haemorrhages around both maculae. The thoracic roentgenogram showed extensive fascicular-focal lesions in both lungs (Fig. 8).

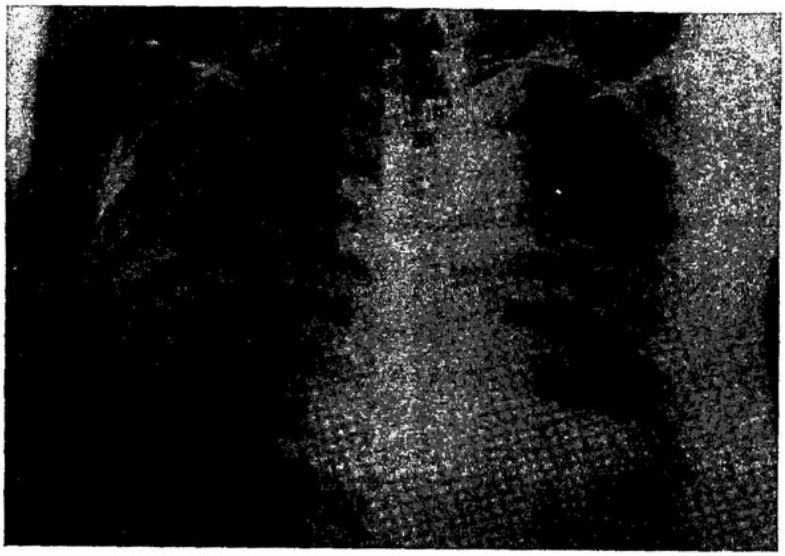


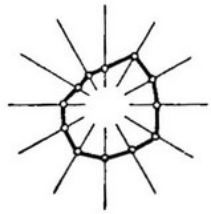
Fig. 8. I. T., male, 36. Malignant nephrosclerosis. Extensive fascicular, focal lesions in both lungs

Capillary tests:

Rumpel-Leede	positive
Göthlin	negative
Borbély	20 Hgcm

Coagulogram:

Bleeding time	120″
Clotting time	4′ 30″
Retraction	normal
Recalcification	280″
Prothrombin time	14″ 100%
Serum effect	21%
Prothrombin consumption	29″
Thrombin time	23″
Toluidine blue time	13″
Thrombin inactivation	0.36 dm
Thrombocyte count	300 000
Fibrinogen	490 mg%
Fibrinogen B	++
Euglobulin lysis time	405′



TEG

r 6′45″
k 2′37″
mε 257

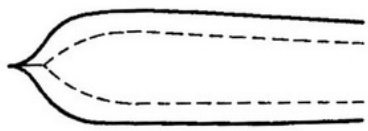


Fig. 9. I. T. Reduced fibrinolysis, hyperfibrinogenaemia and diminished prothrombin consumption. The TEG points to hypercoagulability

Laboratory: red count, 2 000 000; haemoglobin, 7.0 g/100 ml; specific gravity of urine, 1008 to 1012; protein excretion, 12.5 g/24 hrs. Addis counts: red corpuscles, 8 000 000; white corpuscles, 180 000 000; casts, 200 000. Bacteriological examinations negative. NPN, 112 mg/100 ml; serum creatinine, 5.64 mg/100 ml; endogenous creatinine clearance, 2.5 ml/min.

Data regarding coagulation and capillary permeability are shown in Fig. 9. Marked decrease in fibrinolytic activity, pronounced elevation of the level of plasma fibrinogen and the values of TEG pointed to a thrombotic tendency, while

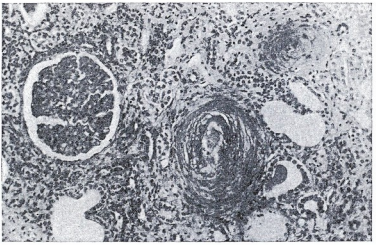


Fig 10. I. T. One of the arterioles is constricted by intensive intimal proliferation, the other shows hyaline obliteration. Note large glomerulus and patent capillaries. Haematoxylin-eosin, × 160

an increase of recalcification time and decrease of prothrombin consumption indicated the existence of bleeding tendency. That the Rumpel-Leede test was positive pointed to the presence of a vascular factor in the development of uraemic haemorrhage. The patient died in uraemic coma.

Diagnosis: malignant nephrosclerosis and pulmonary haemorrhage.

Post mortem: the cut surface of the compact lung displayed lentil- and millet-sized dark patches which gave the Prussian blue reaction. Microscopically chronic alveolar epithelial proliferation, desquamation and haemosiderin were seen in the foci. Patches of fresh haemorrhage were also visible. The left renal artery was plugged by organized thrombus. Histological examination of the kidney disclosed serious arteriolar nephrosclerosis (Fig. 10).

Discussion

The three cases described in the foregoing are illustrative of the differential diagnostic problems which arise most frequently in connection with nephropathies associated with pulmonary haemorrhage. Our case 1 was a typical one of Goodpasture's syndrome. Case 2 was of lupus nephropathy with pulmonary haem-

orrhage, while case 3 was diagnosed as malignant nephrosclerosis accompanied by pulmonary haemorrhage. According to the present state of knowledge, cases 2 and 3 have to be sharply distinguished from the typical form of Goodpasture's syndrome [27, 37, 41, 52, 53]. This is clinically not always practicable as shown by the fact that the so-called "Goodpasture syndrome" has repeatedly been diagnosed in connection with various kidney diseases [12, 21, 32, 36, 40]. Scheer and Grossmann [50] suggest that perhaps not even Goodpasture's [16] case would satisfy the present severe criteria of this disease. Renal and pulmonary biopsy, supplemented later by immuno-histological examinations, are useful for diagnosis in vivo [3, 13, 27, 54, 56]. The true pathogenesis of the nephrotic syndrome in case 2 was elucidated only several years after onset. The establishment of the diagnosis was facilitated by coagulation studies. Case 3 displayed all clinical signs of Goodpasture's syndrome, and even haemosiderosis was found in the lungs.

Conditions of coagulation and capillary permeability merit particular attention in Goodpasture's syndrome, and it is surprising that literature contains comparatively few reports in this respect. According to Benoit et al. [4], it was only in 24 of the 52 cases reported until 1963 that conditions of clotting were studied. Bleeding time, clotting time, thrombocyte count, prothrombin time and the results of the tourniquet test were normal in all cases. Proskey at al. [41] reviewed further 56 cases in 1970 without mentioning coagulation defects. Recently, Everett et al. [14] have found a case with normal fibrinogen level. The bleeding time was protracted in two cases of Duncan et al. [13], while Wayne [61] described a case in which the blood of the patient contained an anticoagulant agent.The tourniquet test was positive in one of the five cases described by Rusby and Wilson [46].

Hypercoagulability in our case was substantiated by hyperfibrinogenaemia, a pronounced reduction of fibrinolysis in the plasma and the characteristic course of the TEG.

Among the kidney diseases hyperfibrinogenaemia occurs most frequently in the nephrotic syndrome [1, 15, 20, 58]. It is noteworthy in this respect that in our case hypoalbuminaemia and the development of an oedema of about 10 litres, were observed. According to Bloom et al. [5] Goodpasture's syndrome may be associated with nephrosis. In four of their five cases nephrosis was observed, and three of these four patients had venous thrombosis. The formation of thrombi is attributed to steroid therapy generally employed in cases of nephrosis [17, 28, 35, 57, 60]. Our observations do not support this concept [20]. We observed the severest hypercoagulability prior to steroid treatment.

The time of euglobulin lysis depends, as has been repeatedly pointed out by McNicol et al. [33, 34], among others on the concentration of fibrinogen. Yet, in our case of Goodpasture's syndrome the prolongation of euglobulin lysis time cannot be entirely blamed on hyperfibrinogenaemia because fibrinolysis was still strongly inhibited although the fibrinogen level of the plasma had dropped below the normal value.

Hypofibrinogenaemia in the terminal phase must have been caused by intravascular clotting. Protracted thrombin time and recalcification time as also the accelerated rate of thrombin inactivation and a weakening of the coagulation-accelerating action of the serum, observed at that time, point to an increase in the split products of fibrin degradation. Histological verification of the presence of fibrin thrombi in the alveoli, too, seems to confirm the diagnosis of consumption coagulopathy which, however, does not explain the early appearance of pulmonary haemorrhage.

Our observations seem to indicate that the bleeding tendency in Goodpasture's syndrome must be due to capillary damage and not to coagulopathy. This concept is in harmony with immunological observations that the reaction between antigens and antibodies takes place on the basement membranes [3, 13, 50, 54, 56].

Various forms of coagulopathy occur in cases of SLE [11, 25, 29, 30, 44, 45]. We have shown in an earlier communication [7] that capillaropathy alone may give rise to gross haemorrhage. Thrombocytopenia is nevertheless the most frequent cause of bleeding tendency in SLE. It occurs in 30 to 50 per cent of the cases and is frequently suggestive of ITP [6, 43]. In our case 2, grave thrombocytopenia induced, in addition to various bleedings, massive haemorrhage in the lungs.

Coagulation studies in our nephrosclerotic-uraemic patient revealed hyperfibrinogenaemia combined with a disturbance of prothrombin consumption. A thrombotic tendency of in-vitro coagulation in cases of uraemia has been reported also by other authors [18, 31, 62]. It was stated by us in 1968 that the level of plasma fibrinogen is often elevated in uraemia [8]. In our case 3, pulmonary haemorrhage was attributable to decreased prothrombin consumption and increased capillary permeability. The decrease in prothrombin consumption has to be attributed to reduced thromboplastin production, probably due to thrombocytic dysfunction which is now regarded by an increasing number of authors as the most important factor responsible for the bleeding tendency in uraemia [24, 47, 55].

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