PART XIX

*Guest Lecture*  COAGULATION AND RENAL DISEASES

*Chairmen*  
H Thaysen  
S Casado
COAGULATION AND RENAL DISEASES
A Kanfer

CHU Bichat, Paris, France

A great number of renal diseases are associated with disturbances of the coagulation-fibrinolysis system. On one hand intravascular coagulation certainly leads to acute renal failure in laboratory animals and probably plays a pathogenetic role in numerous human situations. On the other hand certain renal diseases or syndromes are per se apt to induce more or less severe haemostatic disturbances characterised by either a bleeding tendency or a hypercoagulable state. Obviously a comprehensive review of the field is beyond the scope of this article but I will consider the following points: 1) intravascular coagulation and acute renal failure (ARF), 2) role of intravascular coagulation in rejection of renal transplants, and 3) the hypercoagulable state induced by the nephrotic syndrome and acute uraemia.

INTRAVASCULAR COAGULATION AND ARF

Some years ago, intravascular coagulation was considered an important intermediary mechanism in the pathogenesis of ARF; now it appears somewhat discarded and a brief restatement of the question – from both experimental and clinical points of view – may be timely.

Experimental ARF induced by intravascular coagulation: the role of fibrinolysis inhibition and of vasoactive phenomena

Pure disseminated intravascular coagulation, induced by thrombin or thromboplastin infusion is unable to induce severe and lasting renal damage and failure [1,2]. In fact thrombin infusion is only followed by transient renal fibrin deposits [1,3]. This appears to be due mainly to efficient glomerular fibrinolytic activity (GFA), that is the release of plasminogen activator by glomerular cells followed by the enzymatic action of plasmin on fibrin. With Sraër and other colleagues in Professor Richet’s department we assessed quantitatively GFA of isolated rat glomeruli, either by the fibrin slide technique [3] or by counting
radioactivity of fibrin degradation products (FDP) released in $^{125}$I fibrin coated tubes [4]. In the first set of experiments, we observed that when nephrectomy was performed immediately after thrombin infusion massive intracapillary fibrin thrombi were present, with a GFA almost four-fold greater than in control rats, fibrinolytic activity having probably been stimulated by ischaemia and stasis; one hour after the termination of thrombin infusion thrombi were no longer noted and GFA had returned to control values. However, when epsilon-aminocaproic acid (EACA) was administered along with thrombin, thrombi persisted in spite of permanently high GFA, probably because EACA directly inhibited the effect of plasmin on fibrin in vivo. In the second set of experiments we demonstrated that GFA was positively correlated with pH, an observation suggesting that, in vivo, acidosis might have an inhibiting effect on cortical fibrinolysis.

Activation of vasomotor systems is also of prime importance in thrombin-induced experimental renal diseases; concomitant injection of angiotensin or epinephrine is essential for the promotion of massive permanent intrarenal fibrin deposition and renal failure [2,5]; Saralasin completely prevents the occurrence of acute renal failure after infusion of thrombin with an antifibrinolytic drug [6]. Finally, the degree of renal failure correlates well with that of fibrin deposition; moreover, according to various experimental protocols, renal lesions extend from moderate tubular necrosis to complete bilateral cortical necrosis [5], suggesting the absence of a clear-cut division between these two lesions. In more complicated forms of DIC-induced ARF, inhibition of fibrinolysis and vasoactive phenomena are also implicated. In the generalised Shwartzman reaction cortical fibrinolytic activity disappears after the first injection of endotoxin [7,8] and cortical necrosis is prevented by alpha-adrenergic blockade [9]. In glycerol haemoglobinuric ARF, cortical necrosis occurs in rats receiving EACA; sympathectomy prevents intrarenal fibrin deposition and renal lesions [10].

Intravascular coagulation and human ARF due to acute tubular necrosis or bilateral cortical necrosis

*Diagnosis of intravascular coagulation*

Diagnosis of clinical intravascular coagulation relies upon the demonstration of the effects of active circulating thrombin, i.e.: 1) activation and consumption of platelets, factor V and factor VIII; 2) transformation of fibrinogen to fibrin monomers and fibrin, with hypofibrinogenemia; 3) presence of fibrin and platelet thrombi; 4) release into the circulation of fibrin degradation products (FDP), resulting from secondary, purely local, fibrinolysis (euglobulin lysis time being normal). Clinical conditions associated with intravascular coagulation are multiple and often complicated and unfortunately there is not a unique diagnostic criterion. Schematically a diagnosis of intravascular coagulation is made or presumed in either of the two following circumstances: 1) evidence of overt consumption coagulopathy, indicating acute disseminated intravascular coagulation (DIC), although massive local intravascular coagulation may lead to
similar systemic haemostatic disturbances, 2) presence of high values of blood FDP and/or fibrin monomers (assessed by ethanol-gelation test or protamine test), associated with histological demonstration of fibrin thrombi, indicating progressive (subacute) intravascular coagulation which may be disseminated or localised.

**ARF with acute DIC**

Acute DIC with overt consumption coagulopathy is present in five to 30 per cent of patients with ARF, the prevalence of DIC being especially high in obstetrical ARF [11–16]. The main conditions leading to this clinical association appear in Table I. The well known severity of such situations is due to both the haemorrhagic and thrombotic consequences of intravascular coagulation. Thus in patients having ARF with DIC, severe protracted circulatory shock, cutaneous and mucous membrane haemorrhages and necrosis and arterial occlusions are strikingly frequent features [11,13,15]; moreover pulmonary oedema or acute coronary syndromes during the so called ‘obstetrical shock’ is probably due to the pulmonary vasoconstriction triggered by circulating fibrinopeptides, fibrin-monomers and FDP [17–19]. Finally DIC affects the outcome of patients with ARF by enhancing frequency of permanent renal sequelae (chronic post-acute renal failure) and mortality (at least in obstetrical condition). Persisting renal insufficiency might be due to partial bilateral cortical necrosis at times demonstrated by arteriography or renal biopsy [20].

**Pathophysiology role of intravascular coagulation in human ARF**

Presumption of a pathogenic role of intravascular coagulation in acute tubular necrosis or cortical necrosis depends on the answers to the following questions:
1) may (disseminated) intravascular coagulation appear as the single (or main) cause preceding the onset of ARF, 2) do serum and urinary FDP indicate intrarenal intravascular coagulation, 3) is there compelling histological evidence of intravascular coagulation in such cases, and 4) is it possible to correlate intravascular coagulation phenomena with acute renal failure?

**DIC preceding ARF** DIC precedes onset of ARF in the absence of any other known cause of renal insufficiency, notably shock or nephrotoxins, in instances such as: severe infections [21], neoplastic diseases [22,23] acute pancreatitis [21], pre-eclamptic toxaemia and abruptio placentæ [20,25–27]. Table II is a summary of the history of four obstetrical patients in whom DIC appeared as the main factor of ARF, due to histologically proved ATN in two of them; the microangiopathic anaemia was probably a direct consequence of DIC [22].

**TABLE II. Acute renal failure related to disseminated intravascular coagulation in four pregnant (29 to 35 weeks) patients with spontaneous complete recovery**

<table>
<thead>
<tr>
<th>n</th>
<th>Toxaemia</th>
<th>Haemolytic anaemia</th>
<th>Platelets (X1000/mm3)</th>
<th>Factor V plasma value %</th>
<th>Fibrinogen plasma value %</th>
<th>Renal pathology</th>
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<tr>
<td>1</td>
<td>+</td>
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<td>60</td>
<td>28</td>
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<td>2</td>
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<td>3</td>
<td>+</td>
<td>+</td>
<td>60</td>
<td>42</td>
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**Significance of fibrin-fibrinogen degradation products in ARF** More than half of the patients with ARF have high serum and urinary FDP values [28–30] even in the absence of consumption coagulopathy; the meaning of this anomaly is still subject to controversy [31,32]. Systemic fibrinolysis being excluded in ARF as the euglobulin lysis time is normal [13] – serum FDP arise from the local lysis of fibrin deposits; a renal origin is demonstrated, in some patients, by a FDP value being greater in renal vein than in the renal artery [15]. Urinary FDP might theoretically reflect 1) lysis of intrarenal fibrin deposits or 2) filtration of serum FDP by glomeruli or 3) filtration of fibrinogen subsequently split by urokinase. The latter hypothesis is unlikely since urinary urokinase activity is low or abolished during ARF [33]. Moreover DIC per se is accompanied by urinary excretion of low molecular weight FDP (E product), while in ARF (with or without DIC) urine contains mainly high molecular weight products, probably indicating intrarenal lysis and ‘active’ disease [30].

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Histological evidence of intravascular coagulation in ARF  In acute tubular necrosis intra-arteriolar and intraglomerular fibrin deposits are occasionally found [28,34,35]. There is no agreement concerning the actual frequency of this finding: the high incidence (about 40 per cent of the patients having renal biopsy) observed by Clarkson et al [28] and Conte et al [15] has not been confirmed in a recent study of Solez et al [36] who demonstrated renal fibrin in only seven per cent of the patients. In bilateral cortical necrosis, on the contrary, massive fibrinous thrombosis of the microvasculature and glomeruli is present in the vast majority of patients [20,37].

Correlations between intravascular coagulation, renal lesions and ARF

In bilateral cortical necrosis, parenchymal destruction is best explained by a massive reduction or abolition of cortical blood flow [20]. Pathogenicity of microvascular thrombosis is strongly suggested by the parallelism in the severity of renal thrombi, glomerular destruction and renal functional impairment [20]. In human acute tubular necrosis the pathophysiologic role of intravascular coagulation is not as well defined. Finally it must be emphasised, in keeping with the statements of Vassalli and Richet [38], that the same aetiologic circumstances may lead to acute tubular necrosis as well as to bilateral cortical necrosis. Probably in both cases cortical ischaemia induced by vasoconstriction is the initial event. In patients having acute tubular necrosis, serum and urinary FDP, and occasional renal fibrin deposits or platelet aggregates indicate minor intravascular coagulation, which may add some degree of mechanical obstruction to the reversible functional vasomotor disturbance characteristic of this situation; in other cases massive intravascular thrombosis occurs and leads to irreversible parenchymal destruction and bilateral cortical necrosis. Several causal factors might in these cases account for the extensive nature of intravascular coagulation in cortical necrosis: inhibition of fibrinolysis induced by pregnancy or antifibrinolytic drugs; DIC of abrupt onset; protracted shock with stasis favouring local thrombosis; hypercoagulability of pregnancy or the post-operative period; and severe metabolic acidosis with decrease of glomerular fibrinolytic activity.

Therapy of ARF associated with disseminated intravascular coagulation

So far there is no definite proof that heparin therapy is beneficial in ARF associated with DIC; the treatment of the underlying disorder is apt to reverse per se haemostatic disturbances [13]; nevertheless heparin therapy has been reported to induce the incidence of ultimate renal sequelae following an episode of DIC [12,15]. Finally management of ARF with DIC might rely upon the following (somewhat subjective) principles 1) heparin is not indicated when the underlying disease or condition (e.g. shock, sepsis, pre- eclamptic toxaemia) is curable by treatment of the underlying aetiology; moreover anticoagulant therapy is obviously dangerous when a local cause of bleeding is present (e.g. peptic ulcer, recent operation) 2) heparin must be given when a therapeutic manoeuvre may trigger or aggravate intravascular coagulation: uterine curettage, chemotherapy
of acute promyelocytic leukaemia (platelet transfusion must also be given in such
cases). 3) a trial of heparin therapy may also be undertaken when underlying
disease is not rapidly amenable to efficient treatment as during certain neoplastic
diseases and haemolytic anaemias.

INTRAVASCULAR COAGULATION AND HUMAN RENAL ALLOGRAFT
REJECTION

Hyperacute rejection

In hyperacute rejection occurring in patients presensitised against donors antigens,
the pathogenic role of intravascular coagulation is indisputable. Indeed the hall-
mark of this situation is massive thrombosis of graft arteries, arterioles, peri-
tubular and glomerular capillaries, eventually leading to cortical necrosis of the
transplanted kidney (Figure 1). Thrombi are made of fibrin and platelet aggre-
gates [39–42]. In this situation, platelets and factors II, V, VIII and fibrinogen

Figure 1. Human hyperacute renal allograft rejection. Multiple intraglomerular and intra-
arteriolar thrombi (arrows) with cortical necrosis (Masson trichome stain). By courtesy
of Docteur L Morel-Maroger

are sequestered in the allograft to such an extent that systemic depletion of
clotting factors may occur, thus mimicking disseminated intravascular coagula-
tion. This condition may be reproduced in animals by xenografts [43].

Graft vascular endothelium is the target of complement dependant cytotoxic
antibodies in hyperacute rejection. Endothelial lesions are apt to trigger several reactions leading to intravascular coagulation: release of factor VIII, von Willebrand factor, provoking platelet adhesion [44]; release of thromboplastin; activation of Hageman factor and aggregation of platelets, owing to their contact with subendothelial structures.

**Acute rejection**

By comparison with hyperacute rejection, the role of intravascular coagulation in acute rejection is much less clear-cut, notably because overt consumption coagulopathy is not a feature of this condition [45].

**Histological findings**

Glomerular capillary lumina are often filled with platelet clumps and fibrin deposits; in some cases such abnormalities are mild and are only found by electron microscopy [41,46]. Immunopathologic studies disclose deposition of fibrin and factor VIII-Ag in glomeruli and renal arterial vessel walls [47]. Interestingly the platelets are intact during reversible rejection episodes while membrane disruption and platelet degranulation are present in cases of irreversible rejection. Renal cortical fibrinolytic activity is diminished or even abolished, the lowest activity being associated with the most severe renal lesions [48].

**Laboratory data**

Fibrin-fibrinogen degradation products (FDP) are almost always found in the urine of patients acutely rejecting renal transplants [30,31,49–51]; concomitantly urine may contain factor VIII antigen. Urinary FDP may be simply markers of acute tubular necrosis during the first two weeks following transplantation; their predictive value at this time for the diagnosis of rejection is questionable [31,50,51]; afterwards there is a close correlation between the appearance of urinary FDP and the onset of acute rejection; urinary FDP may even announce the rejection episode as they are sometimes detectable several days before clinical signs. Therefore it has been recommended to search systematically and regularly for their presence in transplanted patients [51]. Increase of serum FDP values is less consistently found during acute allograft rejection [29,30,50,52]; again the diagnostic value of this abnormality appears greater when found more than two weeks after transplantation [52]. Numerous laboratory data support the participation of platelets in the pathogenesis of acute rejection, in keeping with the histological findings cited above: a) radio labelled platelets accumulate in the rejected kidney [53–55], b) platelet survival is shortened [56], c) activation of circulating platelets occur, as indicated by release of platelet-factor IV and enhanced bioavailability of platelet factor III [56,57], d) urinary immunoreactive thromboxane B2 is increased [58]. Each of these abnormalities disappear when the rejection episode is reversed by successful steroid treatment.
Pathophysiology

Most probably intrarenal immunological injury triggers activation of the coagulation system and platelets. Thus, immune complexes, which are often found in patients undergoing acute rejection and having fibrin deposits in graft microvasculature [59], may activate Hageman factor [60]; also they induce complement-dependant profound platelet changes: availability of procoagulant factor III [61], platelet aggregation with subsequently release of histamine and serotonin [62,63] and release of platelet factor IV. Renal cortical ischaemia is a major finding of renal failure in acute allograft rejection [64]: conceivably the coagulation system may participate in this abnormality via serotonin induced vasoconstriction and direct mechanical obstruction by fibrin and platelet thrombi.

Anticoagulant therapy in acute renal transplant rejection

There is no proof for a favourable effect of heparin or antiplatelet therapy given for acute rejections in man; indeed in such cases increasing dosage of corticosteroids alone is sufficient to reverse the rejection episode. In a controlled study the outcome of renal transplants and notably the incidence of rejection episodes were similar in the group of patients receiving dipryridamole and prednisone by comparison to patients receiving only prednisone [56]. This fact, and also the steroid-induced recovery of platelet abnormalities, is evidence that activation of platelets is a secondary event depending on the immunological injury and is reversible along with it.

HYPERCOAGULABILITY OF THE NEPHROTIC SYNDROME AND ACUTE URAEMIA

Nephrotic syndrome

Thromboembolic diseases

Thrombotic episodes often complicate the course of illness in children or adults with the nephrotic syndrome [65–67]. We [65] and others [68] observed a prevalence of almost 30 per cent of thromboembolic phenomena in these patients, with a predominance of peripheral phlebitis and renal vein thrombosis; more rarely thrombosis affects intracranial veins, or arteries [65,69]; eventually it may be directly responsible for death. Such accidents occur in patients with any type of glomerular disease [65], although renal vein thrombosis occurs mainly, but not exclusively, in patients with membranous glomerulonephritis [65,70]. Since renal vein thrombosis may be unilateral it appears as a consequence and not as a cause of the nephrotic syndrome.

Blood hypercoagulability and the responsibility of nephrotic syndrome in its genesis

Blood disturbances denoting a tendency towards hypercoagulability exist in most patients with the nephrotic syndrome, concerning platelets, clotting factors and
inhibitors of coagulation. The platelet count is elevated, sometimes up to almost one million per ml [65] and platelet hyperaggregability has been noted [68]. Plasma fibrinogen is most often elevated (at times reaching 1g/dl or more) [65, 66] probably owing to exaggerated hepatic synthesis [71]. Factor VIII-coagulant activity is much increased (up to 700%) [65,66], as are, also, in some patients other plasma clotting factors. Antithrombin III activity and antithrombin III antigen are decreased, because of the urinary loss of that inhibitor of low molecular weight (approximatively 65,000) [67,72]: a negative correlation is observed between plasma antithrombin III antigen and antithrombin III clearance [72]. However we noted enhancement of total plasma progressive antithrombin activity, titrated by the thrombin remaining after incubation in heat-defibrinated plasma [65]. This observation was recently confirmed by Boneu and co-workers [73], who, moreover, demonstrated that while indeed antithrombin III and alpha-1-antitrypsin were decreased, alpha-2-macroglobulin (the third inhibitor of thrombin) was readily increased, thus ‘overcompensating’ antithrombin III deficiency.

The nephrotic syndrome per se appears responsible for these haemostatic disorders. Thrombocytosis is present in nephrotic patients, whatever the glomerular disease [65]. Even more convincingly, plasma fibrinogen is negatively correlated with albuminaemia and positively correlated with lipidaemia [65], the same holds for total antithrombin activity [65]. Whereas, as expected, the inverse is true for antithrombin III. Likewise, platelet hyperaggregability after stimulation by arachidonic acid depends upon hypoalbuminaemia [74].

Relation of hypercoagulability to thrombosis

We found that factor VIII coagulant activity was greater in nephrotic patients affected with thromboses than in non-affected patients [65]. Other authors were also able to correlate increase in coagulation factors with an increased frequency of thromboembolic phenomena [66]. Some authors [67,72] related the augmented risk of thrombosis during the nephrotic syndrome to antithrombin III deficiency, but recently Boneu et al noted that no thrombotic complications occurred in nephrotic children with very low antithrombin III values [73]. Finally definite proof of a pathogenic role of ‘hypercoagulability’ in the onset of thrombotic accidents is lacking; however it is conceivable that a combination of an elevated platelet count and concentration of several coagulation factors, with platelet hyperaggregability, enhances the thrombotic risk in nephrotic patients with other predisposing factors such as reduction of plasma volume, bed rest and hypercholesterolaemia.

The hypercoagulability of acute uraemia

Factor VIII coagulant activity is enhanced, up to two to three times normal [75]; likewise hyperfibrinogenaemia is noted in most patients with ARF [75]. Fibrinolytic activity is diminished, as shown by decreased lysis of fibrin slides by plasma of acutely uraemic patients [75]; also, circulating inhibitors of fibrinolysis are increased: urokinase inhibitors on one hand [75], ‘slow’ plasma

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antiplasmin on the other hand [76]. We have demonstrated the latter abnormal-
ity in most of 20 patients affected with ARF independently of the cause of ARF
and of the presence or absence of disseminated intravascular coagulation [76].
The significance of coagulation fibrinolysis system anomalies in ARF is uncer-
tain. They are probably related to the conditions associated with, or preceding,
ARF as much as to acute uraemia itself; thus post-operative or post-traumatic
protracted infections or inflammatory diseases, increases coagulation factors
and fibrinolysis inhibitors. In any case, such potential hypercoagulability could
favour the occurrence of extrarenal thrombotic episodes which complicate
the course of some 10 per cent of patients with ARF [77,78] and also act as a
nonspecific phenomenon facilitating onset or perpetuation of renal intravas-
cular coagulation.

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