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BLOOD COAGULATION ABNORMALITIES IN THE SCHÖNLEIN—HENOCH SYNDROME IN ADULTS

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23 adult patients with Schönlein—Henoch's syndrome were observed between 1965 and 1976. Nephropathy was noted in 18, gastrointestinal bleedings in 13, thrombosis of legs in 4, cases.

Haemostasis was studied in the successive phases of the process on 185 occasions altogether. The studies included four different capillary tests, thromboelastography, the Gerendás coagulogram, determination of partial thromboplastin time and two platelet-function tests. Additional renal biopsy was performed in 10 cases, mesocolon and skin biopsy in one case each.

The results of at least one of the capillary tests were found positive in each of the patients in some stage of the process. The coagulation status was marked by hypercoagulability either in itself or combined with laboratory signs of hypocoagulability. Immunohistological study of the biopsy specimens revealed glomerular fibrin deposits in 7 cases. On the evidence of the follow-up studies the laboratory tests may be used for the assessment of the activity of the process. The alternatives of local intravascular coagulation (LIC) or of compensated diffuse intravascular coagulation (DIC) are offered for the interpretation of hypercoagulability.

Introduction

The Schönlein–Henoch syndrome (SHs) combines purpuric eruptions on the skin with arthralgia and abdominal symptoms, often in association with nephropathy.

To the symptomatology of the syndrome recognized and described under the name of "peliosis rheumatica" by SCHÖNLEIN [48], HENOCH [30] added gastroenterological features and pointed to a possible involvement of the kidney [31]. It has become clear in the last decades that the main problems of the syndrome resulted from nephropathy [18]. SHsis prevalent in children, most uncommon in adults. In fact, the number of adult patients with renal involvement collected by BALLARD et al. [4] from 9 states of North-America over 15 years amounts to no more than 14 cases; a similar incidence has been reported by French authors [5, 12, 15]. In Hungary, six adult cases have been reported by BOGA [6] and sporadic cases by other authors [3, 8, 14, 39, 46].

We had 23 patients with SHs under observation at the Department between 1965 and 1976. The present study has been concerned with haemostasis in this syndrome and with the relationships between the coagulation abnormalities and clinical course.

Patients and methods

Sixteen of the 23 patients were males, 7 were females, between 15 and 69 years of age, average age being 34.8 years. Skin lesions and arthralgia were present in all of the cases, gastrointestinal symptoms in 13. Nephropathy was found in 18 cases. Three of these patients developed renal failure which developed fatal in one, it was reversible in two cases. One of the patients had an episode of carditis. Clinical recovery ensued in 6, death in 3, residual isolated proteinuria in 4, cases. Ten patients are still under treatment of follow-up, owing to nephropathy of protracted course. All patients had haemorrhagic lesions, distribution of which is seen in Fig. 1. Four patients, on the other hand, developed thrombosis of the legs.

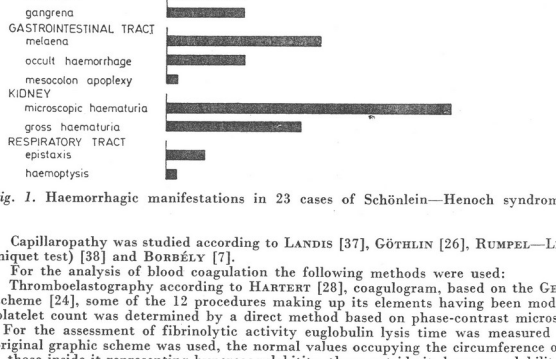


Fig. 1. Haemorrhagic manifestations in 23 cases of Schönlein—Henoch syndrome

Capillaropathy was studied according to LANDIS [37], GÖTHLIN [26], RUMPEL—LEEDE (tourniquet test) [38] and BORBÉLY [7].

For the analysis of blood coagulation the following methods were used:

Thromboelastography according to HARTERT [28], coagulogram, based on the GERENDÁS scheme [24], some of the 12 procedures making up its elements having been modified. The platelet count was determined by a direct method based on phase-contrast microscopy [11]. For the assessment of fibrinolytic activity euglobulin lysis time was measured [33]. The original graphic scheme was used, the normal values occupying the circumference of the circle, those inside it representing hypercoagulabitity, those outside it, hypocoagulability.

Partial thromboplastin time [44], platelet-ADP aggregation [42], platelet factor-3 availability [27] were also studied. Quantitative examination of the urinary sediment belonged to the daily routine [50]. Percutaneous renal needle biopsy was done in 10 cases on 16 occasions, mesocolon and skin biopsy in one case each.

Results

The results of 443 tests in the 23 patients are shown in a column graph, from which the tourniquet test emerges as the most reliable indicator of capillary lesion, it having been found positive in 45% of the cases (Fig. 2). Capillary resistance determined by the method of BORBÉLY was less than 20 Hgcm in 20.8% of the cases. The positivity rate for the two other capillary tests were lower. General capillaropathy was, however, demonstrable in some stage or another of the process in all of the cases.

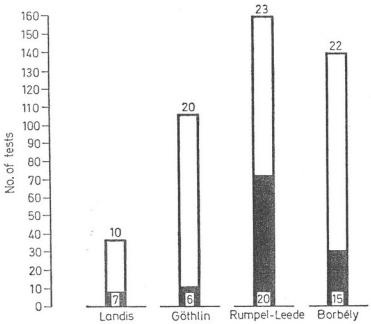


Fig. 2. Results of the capillary tests in 23 cases of Schönlein—Henoch syndrome. The dark areas of the columns indicate the number of studies with abnormal results, the numbers on top of the columns the number of patients

Table I

Results of repeated blood coagulation studies in 23 cases of Schönlein—Henoch syndrome

Method	Normal range	Number of studies			
		Total	Normal	Hyper-coagulability	Hypo-coagulability
Thromboelastogram					
r time	11.4—12.4 min	182	41	114	27
k time	5.5— 6.5 ,,	182	56	86	40
mε (maximal elasticity)	90—150	182	105	68	9
Coagulogram					
bleeding time	100—180 sec	185	185	0	0
recalcification time	180—250 sec	185	149	27	99
prothrombin time	80—110%	185	169	1	15
effect of serum coagulation acceleration	15—25%	185	124	35	26
prothrombin consumption	≥60 sec	185	174	1	10
thrombin time	23—26 sec	185	139	13	33
toluidine-blue time	16—18 sec	185	175	6	4
thrombin inactivation (k)	0.25—0.35 dm	185	119	52	14
platelet count	$150—300 \times 10^3$	185	182	2	1
fibrinogen	200—400 mg/100 ml	185	129	51	5
fibrinogen-B	0	185	123	62	0
euglobulin lysis time	180—240 min	185	33	131	21
Partial thromboplastin time	Control ± 10 sec	142	83	40	19
Platelet ADP aggregation	Control ± 10 sec	117	83	12	22
Platelet factor-3 availability	Control ± 10 sec	113	100	0	13

The results of the blood coagulation and of the platelet function studies are shown in Table I. With the exception of the bleeding time determined according to Duke, none of the parameters studied gave invariably negative results in all phases of the study. It was the TEG which showed the closest association with an abnormal blood coagulation. Of the other parameters, euglobulin lysis time, thrombin inactivation time, labile fibrinogen, fibrinogen

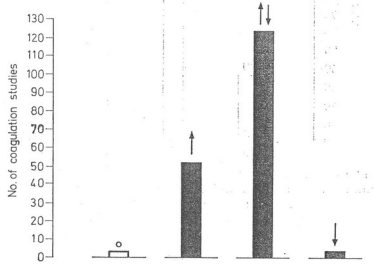


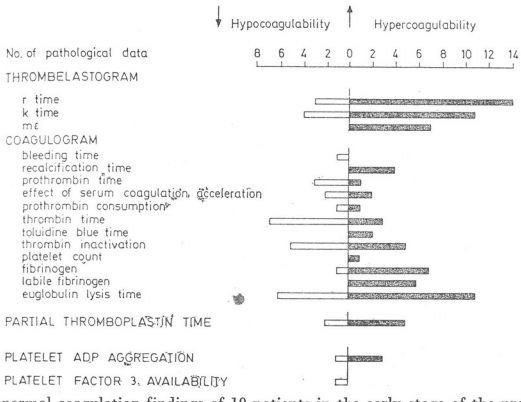
Fig. 3. Results of coagulation studies in 23 cases of Schönlein—Henoch syndrome. 0 = normal coagulability; ↑ = hypercoagulability; ↓ = hypocoagulability; ↑↓ = hyper–hypocoagulability

level and prothrombin time seemed to be most informative of the thrombotic abnormalities, whereas the haemorrhagic abnormalities were the most reliably reflected in the thrombin time.

The changes in the coagulation status of the patients studied on 185 occasions have been represented in Fig. 3. As it can be seen, the totality of all coagulation parameters failed to prove normal on more than three occasions, on the other hand, they consistently pointed to hypocoagulability on four occasions. The prevalent finding was hypercoagulability either in itself or in combination with laboratory evidence of hypocoagulability.

Nineteen patients were subjected to blood coagulation studies in the early stage of SHs or at the times of its recurrence. The abnormal findings are shown in Fig. 4.

Fifteen of 19 patients were brought into clinical remission. Figure 5 shows the results obtained in this stage. Abnormal findings occurred far less frequently at the times of remission than in the periods of activity.



. Abnormal coagulation findings of 19 patients in the early stage of the process or at the time of activity

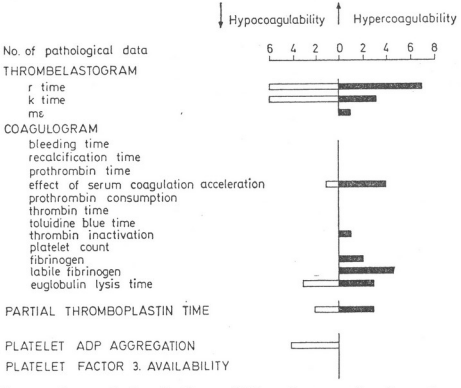


Fig. 5. Abnormal coagulation findings of 15 patients at the time of remission

The results of the follow-up studies are shown in Table II.

Table II

Follow-up of the blood coagulation status in 21 cases

Alterntions in the coagulation status in the course of follow-up	Number of patients
↑ and ↑↓	11
↑↓	7
↑ and ↓ and ↑↓	2
0 and ↑↓	1

0 = normal
↑ = hypercoagulability
↓ = hypocoagulability
↑↓ = hyper — hypocoagulability

The renal biopsy specimen was processed for immunohistological study in 8 cases. Glomerular fibrin deposits were demonstrable by means of fluorescein-labelled antifibrinogen serum in 7 cases. Biopsy of mesocolon or skin performed in individual cases also furnished microscopic evidence of fibrin deposits.

The following case reports exemplify the modifications of haemostasis in the course of the process.

Case 1. Patient D. J., a female aged 56, had been treated for purpuric lesions of the lower extremity at our Department of Dermatology, with prednisolone in daily doses of 20 mg. Microscopic study of the skin revealed fibrin clots (Fig. 6); plasma fibrinogen level was 600 mg per 100 ml. She was referred to our Department of Medicine from there with haematuria. Of the haemostasis parameters the tourniquet test was positive, the r and k times of TEG were reduced, the coagulation studies revealed a decrease in fibrinolytic activity, a protraction of thrombin time and a decrease in the rate of thrombin inactivation. Normality of the toluidine-blue time indicated that the antithrombin effect was unrelated to heparin. Haematuria ceased spontaneously, the tourniquet test became negative and, at a later date, antithrombin activity was no longer demonstrable (Fig. 7). There has been no evidence of any nephrological abnormality since June 1970.

The disappearance of microscopic haematuria thus went hand in hand with normalization of blood coagulation.

Case 2. T. B., a male patient aged 22, had been on steroid treatment prior to admission, but showed still purpuric lesions on his oedematous ankles when first seen by us. Microscopic study of the renal biopsy specimen revealed proliferative focal glomerulonephritis (Fig. 8). The clinical syndrome was marked by considerable microscopic haematuria. Though the capillary tests proved positive, TEG, coagulogram and even the platelet aggregation test pointed to a hypercoagulability. In the course of massive prednisolone doses, the abnormal coagulation parameters assumed a haemorrhagic pattern and were finally normalized, parallel with full clinical normalization (Fig. 9). Purpuric lesions as well as haematuria remained absent in the later course.

Case 3. R. Z., a male patient aged 53, had been referred to our Department of Medicine for purpuric lesions of the lower extremities and a nephrotic syndrome. The presenting symptoms included microscopic haematuria, gross proteinuria and hypalbuminaemia. The microscopic finding revealed an increased lobulation and cell proliferation of the glomeruli and a definite tubular dilatation (Fig. 10). The results of the coagulation studies pointed to a marked hypercoagulability. Capillary resistance and platelet aggregation were reduced. Under the effect of immunosuppressive therapy the nephrotic signs subsided in the presence of persistent coagulation abnormalities (Fig. 11). In the rebiopsy specimen one of the glomeruli showed a fibrosed crescent, another glomerulus was hyalinized (Fig. 12). The extensive morphological

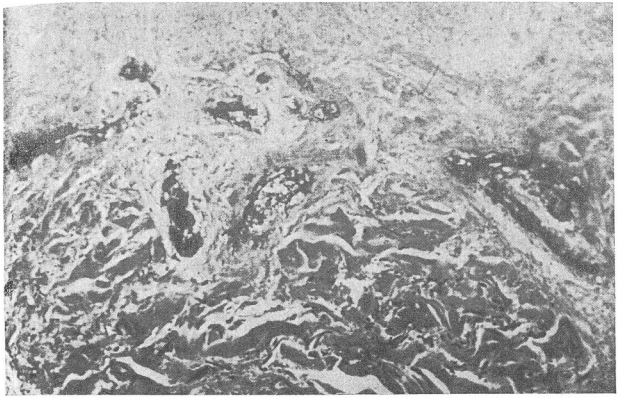


Fig. 6. D. J., female patient aged 56. Microscopic appearance of skin biopsy specimen. Fibrin staining reveals fibrin thrombi in the capillaries of the upper layer of the corium (phosphotungstic acid–HE, ×100)

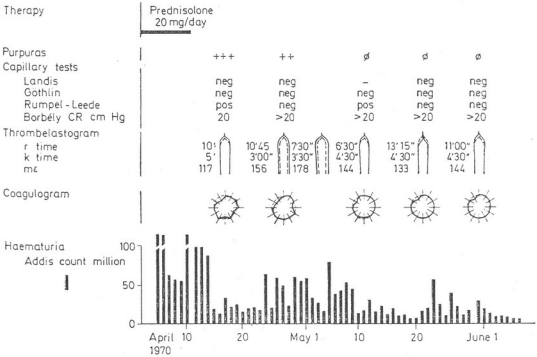


Fig. 7. D. J. Coagulation parameters, referred to the urinary findings. The normal coagulogram and thromboelastogram are represented by an interrupted line. The coagulogram has been represented in accordance with the Gerendás scheme. Parallel with gradual disappearance of haematuria hypercoagulability subsided and the antithrombin effect ceased

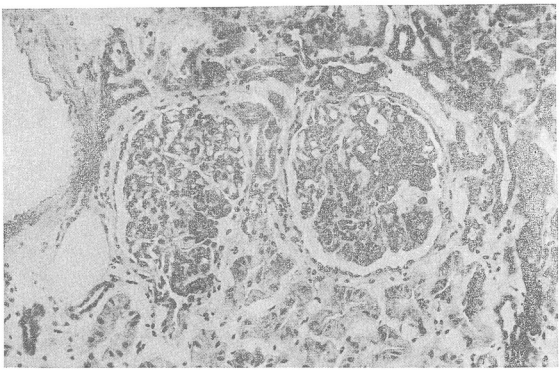


Fig. 8. T. B., male patient aged 25. Light microscopic appearance of renal biopsy specimen. Proliferative focal glomerulonephritis. (HE, ×250)

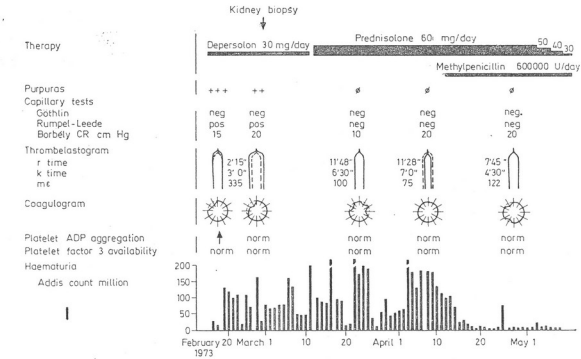


Fig. 9. Clinical course in the same case (T. B.). Considerable hypercoagulability was followed by hypocoagulability reflected in the TEG and soon afterward by disappearance of haematuria. ↑ = increased platelet-ADP aggregation

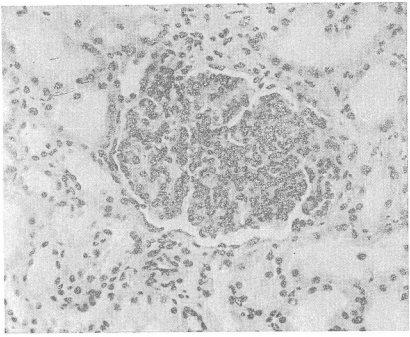


Fig. 10. R. Z., aged 53. Light microscopic appearance of renal biopsy specimen. Glomerular lobulation and cell proliferation. Marked tubular dilatation (HE, ×250)

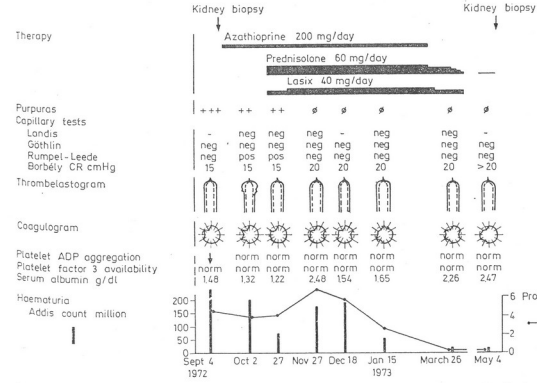


Fig. 11. Relationships between the parameters of haemostasis and the nephrological findings. Under the effect of immunosuppressive treatment during six months marked improvement of the nephrologic findings in the presence of persistent hypercoagulability

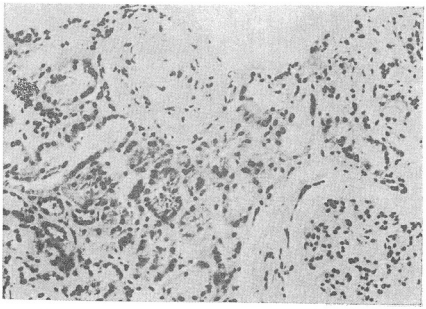


Fig. 12. R. Z. Renal biopsy at the end of immunosuppressive therapy. Deterioration of the glomerular lesions. One of the glomeruli shows hyalinization, another glomerulus shows crescent formation (HE, ×100)

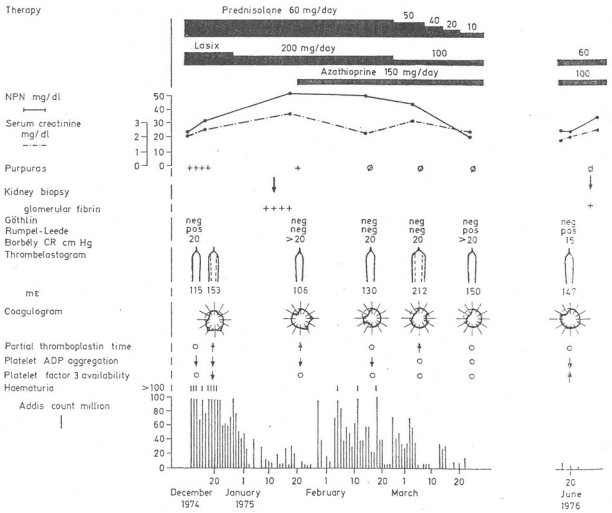


Fig. 13. Clinical course in Sz. F., male aged 52. Under the effect of therapy improvement of coagulopathy and of platelet function deficiency, parallel with decrease of haematuria. ↑ = increase, ↓ = decrease, in platelet-ADP aggregation and in platelet factor-3 availability. 0 = normal function

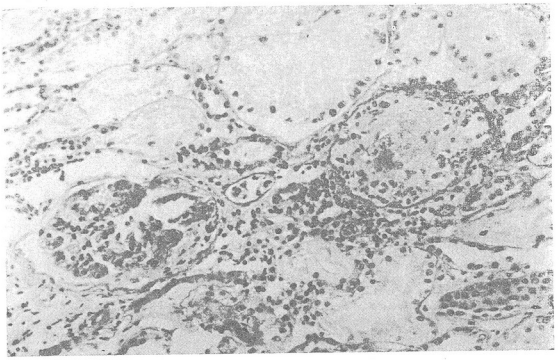


Fig. 14. Patient Sz. F. Light microscopic appearance of the first renal biopsy specimen. Hyalinized glomerulus with epithelial proliferation (HE, ×250)

Fig. 15. Patient Sz. F. Immunofluorescent study of the first renal biopsy specimen. Massive fibrin deposits demonstrable in the epithelial crescent by means of antihuman fibrinogen serum (×550)

lesions were reflected in the coagulation parameters even in the period of clinical remission. The patient is still under our observation. At the present, the renal process shows no signs of activity neither on clinical ground nor on the evidence of renal biopsy. The coagulation abnormalities are very discrete.

In this case persistent hypercoagulability accompanying a deterioration of the morphological abnormalities contrasted with the absence of clinical signs.

Case 4. Sz. F., a male patient aged 52, was admitted with generalized renal oedema and purpura of the extremities, and developed renal failure in the course of hospitalization. On admission, the tourniquet test was positive, the coagulogram revealed a very poor fibrinolytic activity and a marked increase in the levels of fibrinogen and labile fibrinogen. Here, too, as in case 1, an antithrombin effect unrelated to heparin was also noted. The platelet functions were impaired (Fig. 13). He was started on steroids and, after evacuation of retained fluid under the effect of Furosemid, renal biopsy was performed. Light microscopy revealed hyalinization of the majority of glomeruli with extracapillary epithel proliferation (Fig. 14). The immunohistological studies revealed fibrin deposits at the sites of the crescents (Fig. 15). Under the effect of therapy, clinical activity of the process and antithrombin effect were brought under control and the signs of hypercoagulability greatly diminished. The microscopic finding of the rebiopsy specimen one year later was consistent with an inactive chronic glomerulonephritis. His condition has remained satisfactory under the effect of maintenance treatment.

In this case, the severity of the clinical manifestations and of the morphological lesions has subsided, parallel with an improvement of the coagulation disorders, under the effect of combined immunosuppressive therapy.

Discussion

The haemorrhagic disorders in SHs are generally connected in the textbooks with a capillaropathy [43, 45, 49, 54]. The capillary tests are none the less often negative [21], revealing capillary damage in no more than 10 to 25% of the cases [36, 47].

The positivity rate for the total number of the four different capillary tests employed in the present study was 26.6%, however, in some stage or another of the process at least one of the tests proved positive in each patient. No close correlations were found between positive capillary tests and the clinical manifestations of the haemorrhagic disorders. As the diagrams clearly show, in the absence of renal failure systemic capillaropathy subsided earlier than did haematuria.

The general view that coagulation disorders are absent in SHs is based on the prevalence of normal platelet counts, bleeding, clotting and prothrombin times in this syndrome [1, 16, 17, 19, 20, 41, 47]. Detailed coagulation studies are very sparse in the literature and refer to individual cases only [8, 36, 46].

On the evidence of complex coagulation and platelet function studies, coagulopathy not only occurs in, but even seems to be linked with, SHs. A normal coagulation status was found in 2 of the 23 cases in this study. One of these patients came under our observation with isolated proteinuria in an otherwise symptom-free state two years after the acute stage, the other one had only what is termed "peliosis rheumatica", that is, anaphylactoid purpura with no abdominal and renal manifestations. On the other hand, the coagula-

tion system was affected in all cases of SHs with renal or abdominal involvement.

On the evidence of the coagulation studies performed in the successive stages of the process, the period of activity is marked by hypercoagulability. The r and k times of the TEG are reduced, the maximal elasticity of thrombus is increased, and so is the plasma fibrinogen level. The general fibrinolytic activity is generally decreased but may be even abnormally high. Laboratory abnormalities reflecting a haemorrhagic tendency, particularly an antithrombin effect, may be found in some cases. Hypocoagulability manifested itself only when the process was under way of improvement. Discrete coagulation disorders, in particular a minor reduction in fibrinolytic activity or increase in the fibrinogen-B level, may persist even after clinical recovery.

Hypercoagulability was most marked in those cases in which the primary process was associated with a nephrotic syndrome. In one of these cases the plasma fibrinogen level attained 900 mg per 100 ml. The partial thromboplastin time was also generally reduced in this state. Three patients with nephrotic syndrome developed thrombosis of the lower extremities. The prevalence of hypercoagulability in the nephrotic syndrome, to which we called attention earlier [9, 10, 25, 29], is thus also true for the nephrotic syndrome accompanying SHs. This grave coagulation disorder may well be connected in some way with the antigen–antibody reactions and hypercholesterolaemia in the nephrotic syndrome.

Persistent hypercoagulability in case of renal involvement is an adverse prognostic sign. This is exemplified by case 3. In the presence of a marked clinical improvement, persistent hypercoagulability was demonstrable on the evidence of the serial studies, in accordance with extensive damage to the renal tissue revealed by the microscopic study of the biopsy specimen. By contrast, a change towards hypocoagulability may be regarded as a favourable prognostic sign. In case 2, a shift of the coagulation parameters to the side of haemorrhage was followed by rapid improvement and disappearance of all signs of nephropathy.

Intrarenal fibrin deposits were demonstrated in SH nephritis on the evidence of immunohistological and electron microscopic studies by several authors [2, 5, 22, 32, 52]. Intraglomerular fibrin deposits were described by Urizar et al. [53] in the early phase of the process when urinary abnormalities were still absent. On these grounds the authors raise the possibility of intravascular coagulation being involved in the pathogenesis of the process, but neither these nor other authors [51] furnished any evidence in support of this possibility.

Our interpretation for hypercoagulability is basically this: glomerular lesion resulting from an antigen–antibody reaction is accompanied by deposition of fibrin, to which the body responds in the form of increased fibrin

production, that is of hypercoagulability, in all likelihood as a result of a positive feedback mechanism. The laboratory signs of hypercoagulability may thus be connected with a local intravascular coagulation (LIC). Hypocoagulability, on the other hand, may be attributed, in our view, to a counter-regulatory mechanism. In view of the extrarenal manifestation of the SHs, hypercoagulability *in vitro* may well be the consequence of a compensated diffuse intravascular coagulation (DIC).

On the ground of our observations the relationship between coagulopathy demonstrable in SHs and DIC seems similar to that between SHs and purpura fulminans which, according to KOLLER et al. [34, 35] and to other workers [23, 35] represents one of the types of DIC.

The present observations seem to justify anticoagulant therapy in SHs. According to sporadic published evidence, heparin gives benefit in SHs [13]. Anticoagulant therapy, which has its well-known hazards, has to be, obviously, closely explored on the basis of extensive trials until its indications can be reliably established.

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