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nephrotic syndrome prostaglandin endoperoxide formation platelets

Nephrotic Syndrome: Increased Platelet Prostaglandin Endoperoxide Formation, Hyperaggregability, and Reduced Platelet Life Span. Reversal following Remission

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Summary

Nephrotic syndrome is associated with an increased incidence of arterial and venous thrombosis. Platelet function was evaluated in 6 children with active disease (group I) and in 5 children in remission (group II). Platelet malonyldialdehyde in the presence of *N*-ethyl maleimide (1 mM) or thrombin (0.5 unit/ml) was used as an indicator of platelet prostaglandin endoperoxide formation in all patients evaluated, and platelet survivals were performed in 3 of 11. Platelet hyperaggregability was present in group I and was associated with a significant increase ($P < 0.001$) in platelet MDA formation in the presence of either *N*-ethyl maleimide [4.0 ± 0.29 (1 S.D.) nmoles/10^9 platelets] or thrombin (1.77 ± 0.32) when compared to normal controls (3.20 ± 0.26; 1.26 ± 0.18). Other evidence for a "hypercoagulable" state included a marked reduction ($P < 0.001$) in plasma antithrombin III levels to 9.4 ± 3.8 mg/dl (controls, 24 ± 3) and a reduction in platelet life span in both children in whom this study was performed (half-life of 2.1 and 2.5 days). Group II patients in remission did not demonstrate platelet hyperaggregability, and platelet malonyldialdehyde was normal (3.21 ± 0.4; 1.13 ± 0.19). Antithrombin III levels were normal (26.5 ± 4.8), and platelet life-span was normal in both Group II children in whom this parameter was measured (half-life of 3.6 and 4.4 days). The normal half-life of 4.4 days was obtained in the same child in whom a half-life of 2.5 days was present during active disease. Platelet hyperaggregability in this syndrome appears to be due to increased prostaglandin endoperoxide synthesis. Inasmuch as a reduction in plasma antithrombin III levels predisposes to thrombosis and a decrease in platelet survival has been documented to increase the risk of thromboembolism in a number of pathologic states, these findings appear to be of importance in the etiology of hypercoagulability associated with nephrotic syndrome.

Speculation

Platelet hyperaggregability and increased prostaglandin endoperoxide formation is seen in the nephrotic syndrome during disease activity. This platelet hyperfunctional state does not appear to be solely due to concomitant hypoalbuminemia. Other possible factors include a young, reactive platelet population with enhanced functional and thrombogenic potential or the presence of hypercholesterolemia which can be associated with platelet hyperaggregability (25).

Antiplatelet aggregating agents have been used therapeutically in various disease states associated with a shortened platelet life span and an increased risk of thromboembolic complications. These agents may prove to be beneficial in decreasing the incidence of thromboembolic disease in children with the nephrotic syndrome.

An increase in the incidence of thrombosis and thromboembolic phenomena is a well-recognized complication of the nephrotic syndrome. Thrombosis may be either arterial or venous, with renal vein, deep venous, and primary arterial thrombosis occurring both in adults and children during the acute phase of their disease (3, 6, 7, 9, 12, 14–16, 19). In addition, patients with nephrotic syndrome have been shown to have an increased incidence and earlier onset of atherosclerotic vascular disease (4, 20). The cause of this clinical hypercoagulable state has been variously attributed to an increase in circulating plasma coagulation factors (9, 12, 31), a decrease in plasma antithrombin III (10, 11), thrombocytosis (12), or platelet hyperaggregability (1, 22, 32). Recently, Yoshida *et al.* (32), have suggested that platelet hyperaggregability in one patient with nephrotic syndrome may have been related in part to an increased availability of arachidonic acid released from the platelet membrane. We have evaluated the relationship between the presence of platelet hyperaggregability and platelet prostaglandin endoperoxide synthesis in children with the nephrotic syndrome. Platelet survival measurements were also performed because a decrease in platelet life span correlates with clinical hypercoagulable states and the presence of thromboembolic manifestations in various other diseases (8). This report details the results of our studies.

MATERIALS AND METHODS

Blood samples were obtained after informed consent from 6 children with nephrotic syndrome during the active phase of their illness as defined by edema, proteinuria (6.3 to 74.8 g/24 hr), hypercholesterolemia (312 to 1118 mg/dl), and hypoalbuminemia (1.0 to 2.5 g/dl) (Table 1, group I). Five children ranged in age from 5 to 17 years, and all had renal biopsy proven "Nil" Disease or "Minimal Change" Disease. Patient 6 was a 4-day-old infant with biopsy-proven congenital nephrosis who presented with an abdominal mass that on laparotomy proved to be an enlarged left kidney due to the presence of left renal vein thrombosis. None of the other 5 children had any clinical signs of thrombosis or thromboembolic phenomena. After informed consent, evaluations were also performed on five children aged 5 to 13 years with nephrotic syndrome in remission as defined by no clinical edema, proteinuria less than 150 mg/24 hr, serum albumin greater than 3.7 g/dl, and cholesterol less than 220 mg/dl (Table 2, group II). One of the five (patient 5) had been previously evaluated during the active phase of his disease. The majority of the children were on either prednisone or immunosuppressive medication (cytoxan or chlorambucil) at the time of the study (Tables 1 and 2). Except for this therapy, none of the children evaluated had ingested any

other drugs for a period of 10 days before their evaluation. Following informed parental consent, blood samples were obtained by a two-syringe technique and anticoagulated with 0.1 M buffered citrate anticoagulant in a ratio of 9 parts of blood to 1 part of citrate; a clotted sample was also obtained.

Hemoglobin estimations, venous platelet counts, serum albumin, cholesterol, blood urea nitrogen, and creatinine levels were performed by routine techniques. Fibrinogen was assayed by the method of Ellis and Stransky (5), fibrin degradation products (FDP) by the Merskey hemagglutination inhibition assay (17), whereas serum antithrombin III determinations were performed by radial immunodiffusion (Behring). Plasma vitamin E levels were performed by the method of Quaife *et al.* (21).

Platelet aggregation studies were performed as previously described (2), using platelet rich plasma (PRP) prepared by centrifuging the citrated blood at 150 × *g* (800 rpm) at 22°C for 8 min and adjusting the platelet count to approximately 200,000 to 300,000/mm^3. Besides evaluating the PRP for spontaneous aggregation, aggregating agents used included various dilutions of ADP (0.05 to 6 μM), epinephrine (0.005 to 6 μM), and human collagen suspensions. The PRP was kept in full, tightly capped plastic test tubes before use, and all aggregation studies were performed within 120 min of platelet harvesting. Platelet malonyldialdehyde (MDA) formation in the presence of either *N*-ethyl maleimide [NEM (1 mM)] or thrombin (0.5 unit/ml) was used as an indicator of platelet prostaglandin endoperoxide synthesis (28). The contamination of the washed platelet buttons used in the assay was minimal (erythrocytes, <50 per mm^3; leucocytes, <20/mm^3) and was not found to influence the values obtained. Platelet survival measurements were performed by a nonradioisotopic technique (28) in 3 patients with nephrotic syndrome, one of whom had sequential determinations performed at various stages of his illness (patient 5). Platelet survival measurements were also performed on two other children. One was evaluated during the active phase of her illness (patient 3), whereas the other was studied during remission (patient 8). Platelet sizing was performed from blood smears by the method of Rivard and Lazerson (23). Statistical comparison of results was made using the unpaired Student *t* test.

RESULTS

Tables 1 and 2 depict the results of the hemostatic evaluation in children with the nephrotic syndrome during active disease (Group I, patients 1 to 6), and during remission (Group II, patients 5 and 7 to 10), respectively, when compared to normal controls.

PLATELET COUNT, LIFE SPAN, AND SIZING MEASUREMENTS

The mean platelet count in Group I was 288,000 ± 82,000 (1 S.D.) per mm^3 and was not different from the control value of 250,000 ± 50,000/cu mm. The mean platelet count in Group II nephrotics in remission, however, was significantly elevated ($P < 0.005$) to 379,000 ± 162,000/mm^3 when compared to the control group. Platelet survivals were evaluated in 2 children in Group I. A decrease in platelet life span was seen in both children evaluated during the course of active disease. Patient 3 demonstrated a platelet half-life of 2.1 days, and patient 5 had a value of 2.5 days (normal range, 2.9 to 5.9 days). The latter patient when restudied during remission had normalized his platelet life span (half-life of 4.4 days; Fig. 1). One other child was also studied during remission, and platelet half-life was found to be normal at 3.6 days (Table 2, patient 8). Platelet sizing did not reveal any significant differences between the controls or patient groups evaluated.

PLATELET AGGREGATIONS AND MDA FORMATION

In 15 normal children aged 4 to 18 years, irreversible, complete aggregation was not seen below an ADP concentration of 0.8 μM, an epinephrine concentration of 0.2 μM, or with human collagen suspensions at dilutions below 1:32. Also, no spontaneous aggregation was observed. All 6 children in group I demonstrated platelet hyperaggregability with spontaneous aggregation being present only in those children who demonstrated hyperaggregability to all the three aggregating agents (Table 1, patients 1, 3, and 5). All group II children in remission from their disease were normal. Platelet hyperaggregability in group I was accompanied by an increase in platelet MDA formation both in the presence of NEM or thrombin. Mean control values for NEM- (1 mM) or thrombin-induced platelet MDA formation was 3.20 ± 0.26 (1 S.D.) and 1.26 ± 0.18 nmoles MDA per 10^9 platelets, respectively. Platelet MDA in the presence of NEM or thrombin was significantly increased ($P < 0.001$) in group I children with mean levels of 4.0 ± 0.29 and 1.77 ± 0.32, respectively. MDA values in group II were normal at 3.21 ± 0.40 and 1.13 ± 0.19, respectively. Comparison between groups I and II platelet MDA values either in the presence of NEM or thrombin revealed a significant difference at the $P < 0.01$ level.

RESULTS OF FIBRINOGEN, FDP, AND ANTITHROMBIN III ASSAYS

Mean values for fibrinogen was significantly increased ($P < 0.001$) to 466 ± 217 in group I children when compared to the

Table 1. *Evaluation of 6 children with nephrotic syndrome (active disease)*

Parameter measured	Normal values[1]	Patients					
		1	2	3	4	5	6
Platelet count (× 10^3/mm^3)	250 ± 100[2]	295	320	420[3]	237	280	176
Platelet half-life (days)	4.4 ± 1.50	N.D.[4]	N.D.	2.1[3]	N.D.	2.5[3]	N.D.
Spontaneous aggregation (>25% within 10 min)	Absent	+[3]	Absent	+[3]	Absent	+[3]	Absent
Irreversible, >70% aggregation with ADP	≥0.8 μM	0.05[3]	1.6	0.1[3]	0.1[3]	0.05[3]	0.2[3]
Irreversible, >70% aggregation with Epi	≥0.2 μM	0.005[3]	0.01[3]	0.01[3]	0.05[3]	0.005[3]	0.05[3]
Irreversible, >70% aggregation with collagen	≤1:32	1:128[3]	1:32	N.D.	1:128[3]	1:256[3]	1:64[3]
Platelet MDA (NEM) (nmoles/10^9 platelets)	3.20 ± 0.52	4.24[3]	3.65	3.93[3]	3.68	4.36[3]	4.14[3]
Platelet MDA (thrombin) (nmoles/10^9 platelets)	1.26 ± 0.36	2.10[3]	1.77[3]	1.58	1.23	2.04[3]	1.89[3]
Fibrinogen (mg/dl)	250 ± 90	370[3]	410[3]	620[3]	770[3]	490[3]	140
Serum FDP (μg/ml)	<10	1.25	2.5	1.25	2.5	2.5	10
Antithrombin III (mg/dl)	24 ± 6	12.4[3]	7.6[3]	8.4[3]	4.4[3]	15.2[3]	8.4[3]
Plasma vitamin E (mg/dl)	1.27 ± 0.8	1.2	0.9	1.8	2.7	1.1	0.6
Serum albumin (g/dl)	4.3 ± 0.6	1.8[3]	2.1[3]	1.8[3]	1.0[3]	1.7[3]	2.5[3]
Serum cholesterol (mg/dl)	170 ± 50	362[3]	500[3]	1118[3]	319[3]	488[3]	312[3]
Therapy at time of study		P, Ch	P	P	P, Cy	P	

[1] Numbers of controls evaluated varied between 15 and 25, with ages and sex distribution similar to patient groups.

[2] Mean ± 2 S.D.

[3] Abnormal value.

[4] N.D., not done; P, prednisone; Ch, chlorambucil; Cy, cytoxan.

Table 2. *Evaluation of 5 children with nephrotic syndrome (in remission)*

Parameter measured	Normal values[1]	Patients				
		7	8	9	10	5
Platelet count (× 10^3/mm^3)	250 ± 100[2]	605[3]	220	325	485[3]	260
Platelet half-life (days)	4.4 ± 1.50	N.D.[4]	3.6	N.D.	N.D.	4.4
Spontaneous aggregation (>25% within 10 min)	Absent	Absent	Absent	Absent	Absent	Absent
Irreversible >70% aggregation with ADP	≥0.8 μM	1.6	1.6	3.2	1.6	1.6
Irreversible >70% aggregation with Epi	≥0.2 μM	0.4	0.4	0.2	0.4	0.4
Irreversible >70% aggregation with collagen	≤1:32	1:16	1:32	1:32	1:16	1:32
Platelet MDA (NEM) (nmoles/10^9 platelets)	3.20 ± 0.52	3.17	3.65	2.62	3.09	3.51
Platelet MDA (Thrombin) (nmoles/10^9 platelets)	1.26 ± 0.36	1.06	1.35	0.86	1.11	1.29
Fibrinogen (mg/dl)	250 ± 90	200	450[3]	340	235	280
FDP (μg/ml)	<10	2.5	2.5	2.5	2.5	1.26
Antithrombin III (mg/dl)	24 ± 6	20.8	N.D.	32	24.8	28.4
Plasma vitamin E (mg/dl)	1.27 ± 0.8	0.9	0.8	1.0	0.9	1.3
Serum albumin (gm/dl)	4.3 ± 0.6	4.8	4.7	4.5	4.7	4.6
Serum cholesterol (mg/dl)	170 ± 50	197	152	132	200	164
Therapy at time of study		P	P,Ch	P	P	P

[1] Numbers of controls evaluated varied between 15 and 25, with ages and sex distribution similar to patient groups.
[2] Mean ± 2 S.D.
[3] Abnormal values.
[4] N.D., not done; P = prednisone; Ch = chlorambucil; Cy = cytoxan.

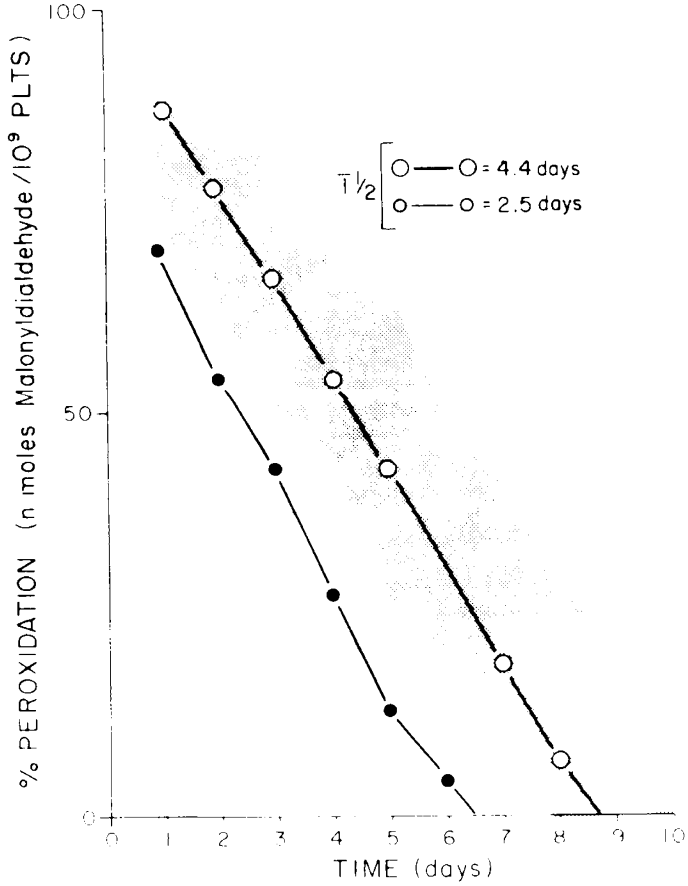

Fig. 1. Platelet survival measurements on a patient with nephrotic syndrome (patient 5) evaluated both during active disease (●) and during remission (○). Platelet half-life was decreased to 2.5 days (normal range, 2.9 to 5.9 days) during the period of disease activity, but had normalized to 4.4 days during remission.

normal value of 250 ± 45 mg/dl. Group II children demonstrated a mean value of 301 ± 98 mg/dl, which was not different from the controls. Assays for serum FDP were within the normal range for both groups (Tables 1 and 2). In group I, the mean antithrombin III level was significantly decreased ($P < 0.001$) to 9.4 ± 3.8 mg/dl when compared to a value of 24 ± 3 mg/dl in the normal controls. Antithrombin III levels in group II were normal at 26.5 ± 4.8 mg/dl. Comparison between the antithrombin III levels in groups I and II showed that the differences in levels were significant at the $P < 0.001$ levels.

RESULTS OF PLASMA VITAMIN E, SERUM ALBUMIN, AND CHOLESTEROL

Mean plasma vitamin E levels in groups I and II were 1.38 ± 0.8 and 0.98 ± 0.2 mg/dl, respectively, and was similar to the control values of 1.27 ± 0.4 mg/dl. As expected, in Group I children with active disease hypoalbuminemia was marked, with a mean value of 1.82 ± 0.50 g/dl when compared to the normal level of 4.3 ± 0.3 ($P < 0.001$).

Group II children were normal with levels of 4.66 ± 0.11 g/dl. Similarly, hypercholesterolemia was a hallmark of group I children with mean levels of 517 ± 306 mg/dl when compared to a normal value of 170 ± 25 ($P < 0.005$). Group II children were normal at 169 ± 29 mg/dl.

DISCUSSION

In this study, children with nephrotic syndrome during the active phase of their disease (group I) manifested platelet hyperaggregability with or without the presence of spontaneous platelet aggregation. The increased platelet sensitivity to aggregating agents was associated with an increased formation of platelet MDA in the presence of either NEM or thrombin. Platelet survival was found to be decreased in 2 of 2 children with active disease during the period of platelet hyperaggregability. Other abnormalities in hemostasis included a reduction in plasma levels of antithrombin III and hyperfibrinogenemia. No abnormalities were found in children (group II) evaluated during remission.

Previous evaluation of hemostasis in patients with the nephrotic syndrome have documented the presence of elevations in the levels of Factors I, V, VII, VIII, and X (9, 12, 31) and a decrease in plasma antithrombin III levels (10, 11). Platelet abnormalities have included thrombocytosis and the presence of platelet hyperaggregability (1, 22, 32). Bang *et al.* (1) in 1973 first documented the presence of enhanced platelet aggregation in patients with active glomerular disease including the nephrotic syndrome. These authors found that the degree of platelet functional abnormality was significantly correlated with the degree of proteinuria and the serum albumin level. Furthermore, they attributed the platelet hyperaggregability to the urinary losses of plasma proteins normally responsible for inhibition of platelet aggregation. Most recently, Yoshida and Aoki (32) have shown that platelet hyper-

aggregability to arachidonic acid and epinephrine in one patient with the nephrotic syndrome was normalized *in vitro* by the addition of albumin to the patient's PRP. This finding has been confirmed by Remuzzi *et al.* (22). The former group of workers also demonstrated that the addition of albumin to washed platelets from normal individuals inhibited collagen-induced aggregation and MDA formation and postulated that albumin inhibited platelet aggregation by binding to released arachidonic acid, thus preventing the arachidonic acid from being metabolized through the platelet prostaglandin pathway.

Arachidonic acid released from platelet membrane phospholipids is metabolized by stimulated platelets to the proaggregatory cyclic endoperoxides PGG_2 and PGH_2 and thromboxane A_2. The cyclic endoperoxides PGG_2 and PGH_2 break down to give a C_{17} hydroxy fatty acid and MDA (24, 27). Smith *et al.* (26) have shown that platelet MDA, a byproduct of the endoperoxides, may be used as an indicator of platelet prostaglandin synthesis. Platelet MDA values have also been demonstrated to be elevated in various pathologic disease states associated with an increased risk of thrombosis including diabetes mellitus (29, 30). Using this assay, we have demonstrated that platelet MDA formation was increased in washed platelets from all 6 patients with nephrotic syndrome evaluated during the active phase of their disease concomitant with platelet hyperaggregability. This finding suggests that the enhanced platelet activity in this syndrome is due to increased platelet prostaglandin endoperoxide formation. The presence of an increase in platelet MDA formation in washed platelets also suggests that other factors in addition to hypoalbuminemia may be involved in the causation of the platelet abnormalities. Inasmuch as immunosuppressive medication was used both in children in groups I and II, this therapeutic modality did not appear to influence the results of the platelet functional assays. We have previously shown that a decrease in plasma vitamin E levels is associated with platelet hyperaggregability (13). Inasmuch as vitamin E levels were normal in both groups I and II, hyperaggregability could not be explained on this basis.

"Hypercoagulability" implies that prethrombotic changes can be detected in blood and that these changes are pathogenetically important for the development of thrombosis or can be used to predict its occurrence. A number of cases of idiopathic venous thromboses have been reported to occur in familial antithrombin III deficiency (8). Thus, the presence of a reduction in the level of antithrombin III in the nephrotic syndrome is of clinical significance and may be an important factor in the development of hypercoagulability in this disease. In evaluating the role of platelet survival and turnover measurements in patients with thromboembolic disorders, a number of investigators have documented a reduction in platelet life span in subgroups of patients with diffuse arterial disease, arterial and venous thrombosis, homocystinuria, vasculitis, valvular heart disease, prosthetic heart valve replacement, arteriovenous shunts, and ischemic heart disease. Moreover, a decrease in platelet survival occurs in those subgroups who develop thromboembolic complications (8). Thus, our finding of shortened platelet survivals in patients with nephrotic syndrome during the active phase of their illness is of possible clinical significance and may identify the patient who is at risk from the development of thrombotic complications. The incidence of symptomatic or asymptomatic thrombosis in this disorder has been variously estimated at 5 to 33%, depending on the methods used for its detection (16, 18). The problem is therefore of clinical importance. A prospective evaluation of platelet survival and function together with thorough evaluation for symptomatic and asymptomatic thrombosis in the nephrotic syndrome appears indicated to more clearly understand these interrelationships.

REFERENCES AND NOTES

1. Bang, N. U., Trygstad, C. W., Schroeder, J. E., Heidenreich, R. O., and Csiscko, B. M.: Enhanced platelet function in glomerular disease. J. Lab. Clin. Med., *81:* 651 (1973).
2. Born, G. V. R.: Aggregation of blood platelets by ADP and its reversal. Nature (Lond.), *194:* 927 (1962).
3. Clarkson, A. R., and Seymour, A. E.: Coagulation and renal disease. Med. J. Aust., *1:* 573 (1976).
4. Curry, R. C., and Roberts, W. C.: Status of the coronary arteries in the nephrotic syndrome. Am. J. Med., *63:* 183 (1977).
5. Ellis, B. C., and Stransky, A.: A quick and accurate method for the determination of fibrinogen in plasma. J. Lab. Clin. Med., *58:* 477 (1961).
6. Goldbloom, R. B., Hillman, D. A., and Santulli, T. V.: Arterial thrombosis following femoral venupuncture in edematous nephrotic children. Pediatrics, *40:* 450 (1967).
7. Gootman, N., Gross, J., and Mensch, A.: Pulmonary artery thrombosis. Pediatrics, *34:* 861 (1964).
8. Hirsh, J.: Hypercoagulability. Semin. Hematol., *14:* 409 (1977).
9. Kanfer, A., Kleinknecht, D., Broyer, M., and Josso, F.: Coagulation studies in 45 cases of nephrotic syndrome without uremia. Thromb. Diath. Haemorrh., *24:* 562 (1970).
10. Kauffman, R. H., deGraeff, J., de la Riviere, G. B., and van Es, L. A.: Unilateral renal vein thrombosis and nephrotic syndrome. Report of a case with protein selectivity and antithrombin III. Clearance studies. Am. J. Med., *60:* 1048 (1976).
11. Kauffman, R. H., Veltkamp, J. J., van Tilburg, N. H., and van Es, L. A.: Acquired antithrombin III deficiency and thrombosis in the nephrotic syndrome. Am. J. Med., *65:* 607 (1978).
12. Kendall, A. G., Lohmann, R. C., and Dossetor, J. B.: Nephrotic syndrome: a hypercoagulable state. Arch. Intern. Med., *127:* 1021 (1971).
13. Lake, A. M., Stuart, M. J., and Oski, F. A.: Vitamin E deficiency and enhanced platelet function: reversal following E supplementation. J. Pediatr., *90:* 722 (1977).
14. Levin, S. E., Zamit, R., and Schmaman, A.: Thrombosis of the pulmonary arteries and the nephrotic syndrome. Br. Med. J., *1:* 153 (1967).
15. Lieberman, E., Heuser, E., Gilchrist, G. S., Donnell, G. N., and Landing, B. H.: Thrombosis, nephrosis, and corticosteroid therapy. J. Pediatr., *73:* 320 (1968).
16. Llach, F., Arieff, A. I., and Massry, S. G.: Renal vein thrombosis and nephrotic syndrome. Ann. Intern. Med., *83:* 8 (1975).
17. Merskey, C., Kleiner, G. J., and Johnson, A. J.: Quantitative estimation of split products of fibrinogen in human serum, relation to diagnosis and treatment. Blood, *28:* 1 (1966).
18. Pollak, V. E., Kanter, A., and Zaltzman, S.: Renal vein thrombosis. Am. J. Med., *17:* 282 (1966).
19. Pollak, V. E., Kark, R. M., Pirani, C. L., Shafter, H. A., and Meuhrcke, R. C.: Renal vein thrombosis and the nephrotic syndrome. Am. J. Med., *21:* 496 (1956).
20. Porro, G. B., and Bianchessi, M.: Ischemic heart disease complicating the nephrotic syndrome. Lancet, *2:* 804 (1969).
21. Quaife, M. L., Scrimshaw, N. S., and Lowry, O. H.: A micromethod for assay of total tocopherols in blood. J. Biol. Chem., *180:* 1229 (1949).
22. Remuzzi, G., Mecca, G., Marchesi, D., Livio, M., de Gaetano, G., Donati, M. B., and Silver, M. B.: Thrombosis and the nephrotic syndrome. Blood, *52* (Suppl. 1): 288 (1978).
23. Rivard, G. E., and Lazerson, J.: A simple method for platelet sizing. J. Lab. Clin. Med., *86:* 547 (1975).
24. Samuelsson, B.: The role of prostaglandin endoperoxides and thromboxanes in human platelets. In: M. J. Silver, J. B. Smith, J. J. Kocis: Prostaglandins in Hematology, p. 1 (Spectrum Publications, New York, 1977).
25. Shattil, S. J., Anaya-Galindo, R., Bennett, J., Colman, R. W., and Cooper, R. A.: Platelet hypersensitivity induced by cholesterol incorporation. J. Clin. Invest., *55:* 636 (1975).
26. Smith, J. B., Ingerman, C. M., and Silver, M. J.: Malonyldialdehyde formation as an indicator of prostaglandin production by human platelets. J. Lab. Clin. Med., *88:* 167 (1976).
27. Smith, J. B., Ingerman, C. M., and Silver, M. J.: Effects of arachidonic acid and some of its metabolites on platelets. In: M. J. Silver, J. B. Smith, J. J. Kocis: Prostaglandins in Hematology, p. 277 (Spectrum Publications, New York, 1977).
28. Stuart, M. J.: Malondialdehyde formation as a measure of platelet survival. In: M. J. Silver, J. B. Smith, J. J. Kocis: Prostaglandins in Hematology, pp. 57–68 (Spectrum Publications, New York, 1977).
29. Stuart, M. J.: Platelet malonyldialdehyde formation: an indicator of platelet hyperfunction. Thromb. Haemostasis *42:* 649 (1979).
30. Stuart, M. J., Elrad, H., Graeber, J. E., Hakanson, D. O., Sunderji, S. G., and Barvinchak, M. K.: Increased synthesis of prostaglandin endoperoxides and platelet hyperfunction in infants of mothers with diabetes mellitus. J. Lab. Clin. Med., *94:* 12 (1979).
31. Thomson, C., Forbes, C. D., Prentice, C. R. M., and Kennedy, A. C.: Changes in blood coagulation and fibrinolysis in the nephrotic syndrome. Q. J. Med., *43:* 399 (1974).
32. Yoshida, N., and Aoki, N.: Release of arachidonic acid from human platelets. A key role for the potentiation of platelet aggregability in normal subjects as well as in those with nephrotic syndrome. Blood, *52:* 969 (1978).

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