Scand J Haematol (1979) **22**, 423–432

The Varied Sensitivity of Partial Thromboplastin and Prothrombin Time Reagents in the Demonstration of the Lupus-Like Anticoagulant

P. M. MANNUCCI, M. T. CANCIANI, D. MARI & P. MEUCCI

Haemophilia and Thrombosis Centre Angelo Bianchi Bonomi, International Training Centre of the World Federation of Haemophilia, University of Milano, Italy

An acquired inhibitor of blood coagulation, similar to that described in patients with Systemic Lupus Erythematosus (SLE), was detected during routine coagulation screening in 10 patients who did not meet the criteria for a diagnosis of SLE. The lupus-like anticoagulant (LLAC) was diagnosed on the basis of prolonged activated partial thromboplastin time (APTT) and/or prothrombin time (PT) which failed to correct when patient plasma was added to normal plasma; an additional criterion was an abnormal tissue thromboplastin inhibition test. No patient had a specific inhibitor directed against factors VIII and IX. Demonstration of LLAC was highly dependent upon the type of reagents adopted in the APTT and PT: the abnormality was detected consistently by one reagent only. One-stage assays of factors VIII and IX were characteristic of the presence of an inhibitor, showing non-parellel dose-response curves or decreased activity at low dilutions which were partially corrected at higher dilutions. Although 7 patients were free of abnormal bleeding, unequivocal signs of haemorrhagic tendency after a surgery were present in the remaining 3 patients. The findings suggest that LLAC is a non-exceptional cause of prolonged coagulation screening tests, and that it may sometimes be associated with impaired haemostasis.

Key words: acquired coagulation disorders – circulating anticoagulants – coagulation inhibitors – partial thromboplastin time

Accepted for publication April 10, 1979

Correspondence to: Dr. P. M. Mannucci, Via Pace 15, 20122 Milano, Italy

Circulating anticoagulants interfering with the activation of prothrombin by the prothrombinase complex (Xa, V, Ca^{2+}, phospholipids) are frequently encountered in patients with systemic lupus erythematosus (SLE) (for review cf. Feinstein & Rapaport 1974). The lupus anticoagulant is usually detected by an abnormal activated partial thrombiplastin time (APTT) and/or prothrombin time (PT) which fail to be corrected when patient plasma is mixed with normal plasma. Recently, the tissue throm-

0036–553X/79/050423–10 $02.50/0

boplastin inhibition test (TTIT) has been proposed as an additional sensitive screening method (Schleider et al 1976). The lupus anticoagulant is clearly distinct from other anticoagulants developing in SLE and other autoimmune disorders, since the inhibition is time-independent and clotting factors are not progressively inactivated.

It is now recognized that this abnormality is not invariably associated with SLE, and that it can occur in association with, or even in absence of, other demonstrable underlying diseases, reviewed by Lechner (1974). During routine coagulation screening of a large series of out-patients, carried out over a period of 2 years, we have encountered 10 cases without clinical or laboratory evidence of SLE having in vitro coagulation abnormalities similar to those of the lupus anticoagulant and suggesting that lupus-like anticoagulants (LLAC) are not uncommon. The observation that a number of these patients had a mild but consistent bleeding tendency prompted us to carry out more extensive clinical and laboratory investigations which form the basis of this report. Since the available PT and APTT reagents are probably not equally sensitive to the LLAC abnormalities, we also decided to compare a variety of commercial methods used for routine coagulation screening in order to evaluate their capability to detect the anticoagulant.

MATERIAL AND METHODS

Patients. Of 813 subjects referred over a period of 2 years to the Haemophilia and Thrombosis Centre for coagulation screening tests 10 patients (7 females and 3 males) were found to have a prolonged APTT. The lack of APTT correction when their plasma was mixed with equal parts of normal plasma and an abnormal tissue thromboplastin inhibition test (TTIT) were adopted as diagnostic criteria for LLAC. After detection of the anticoagulant, patients underwent detailed coagulation studies, as well as clinical and laboratory investigations to assess a possible diagnosis of SLE following the criteria of the American Rheumatism Association Section of the Arthritis Foundation (1973).

Screening coagulation studies. Bleeding time, platelet count and thrombin time were carried out as described by Denson (1976). The APTT was performed routinely with a method employing the platelet substitute Thrombofax (Ortho) diluted 1:4 in tris buffer and light kaolin (5 g/l in tris buffer) (Refsum et al 1978). For a period of time APTT was also carried out in this laboratory with the commercial reagent Cephotest (Nygaard, Oslo) (Refsum et al 1978). The prothrombin time (PT) was performed with a standardized extract of human brain (Manchester Comparative Reagent) and the technique recommended by Dr. Poller who supplied the reagent.

Other APTT and PT reagents. Plasma in which LLAC had been detected with the routine APTT methods was also tested with an international reference preparation made available by the National (UK) Reference Laboratory for Anticoagulant Reagents (NRLACR) and with commercial kits manifactured by the following companies: Behringwerke, Bio-Merieux, Boehringer, Dade (Actin), General Diagnostic (Automated APTT), Hyland, Immuno, Nygaard (Cephotest) and Ortho. LLAC plasmas were also studies with 5 commercial tissue thromboplastins derived from rabbit brain (Bio-Merieux, Boehringer, Dade, Ortho and General Diagnostic); with a reagent (Thrombotest, Nygaard) containing ox brain thromboplastin and with a preparation from human placenta (Behringwerke).

Tissue thromboplastin inhibition test. This test, which explores the capacity of LLAC to inhibit diluted tissue thromboplastin, was carried out as described by Schleider et al (1966) with slight modifications. Simplastin (General Diagnostic) was diluted 1:50 with 0.15 M NaCl; 0.1 ml of the dilution was mixed with 0.1 ml of patient plasma, incubated at 37° C for 5 min and added with 25 mM $CaCl_2$. The patient clotting time was divided by the clotting time of reference normal

plasma tested under the same conditions. The calculated ratios were considered abnormal if they exceeded more than 2 SD from the mean ratio observed in 22 healthy subjects (11 male and 11 female) taken as the reference group. The plasma of a patient with a severe intrinsic clotting defect (haemophilia A, factor VIII $< 1\%$) served as an additional control in the test.

Clotting factor assays. Factor VIII (and factor IX) assays were carried out with a one-stage method based on the partial thromboplastin time described elsewhere (Mannucci et al 1976). Factor II (Taipan venon method), factor V (human brain thromboplastin and aged oxalated substrate plasma), factor VII (human brain thromboplastin and congenitally deficient substrate plasma), factor X (Russel viper venon and artificially deficient plasma), and factors XI and XII (Kaolin-APTT system and congenitally deficient substrate plasma) were assayed with methods described by Denson (1976). Specific inhibitors directed towards factors VIII or IX were searched for with a method described elsewhere (Ruggeri 1977).

RESULTS

Clinical findings. After the detection of LLAC, the patients were throughly evaluated for the presence of the following manifestations adopted by the American Rheumatism Association for the diagnosis of SLE: (1) skin lesions (butterfly rash, discoid lupus, Raynaud phenomena, photosensitivity); (2) serositis (either pleuritis or pericarditis); (3) kidney lesions (urinary cellular casts or proteinuria exceeding 3.5 g/dl); (4) leucopenia ($< 4.0 \times 10^9$/l); (5) haemolytic anaemia; (6) thrombocytopenia ($<150 \times 10^9$/l); (7) positive LE test; (8) biologic false-positive serologic tests for syphilis. Rheumatoid factor, antinuclear antibodies and increased γ-globulins were also investigated. Table 1 shows that a great majority of these alterations were not present in the patients, with the exception of thrombocytopenia in 6 cases, positivity of the anti-

TABLE 1

Criteria of the American Rheumatism Association for the diagnosis of SLE

Patient no	Skin lesions	Serositis	Kidney lesions	Leucopenia	Haemolytic anaemia	Thrombocytopenia	LE test	Syphilis tests	Rheumatoid factor	Antinuclear antibodies	Increased γ-globulins
1	−	−	−	−	−	−	−	−	+	+	−
2	−	−	−	−	−	+	−	−	−	+	−
3	−	−	−	−	−	+	−	−	−	−	−
4	−	−	−	−	−	+	−	−	−	−	−
5	−	−	−	−	−	−	−	−	−	−	−
6	−	−	−	−	−	+	−	−	−	−	−
7	−	−	−	−	−	+	−	−	−	−	−
8	−	−	−	−	−	−	−	−	−	−	−
9	−	−	−	−	−	−	−	−	−	−	−
10	−	−	−	−	−	+	−	−	−	−	−

TABLE 2

Main clinical and laboratory findings

Patient no	Sex	Age	APTT ratio	Corrected APTT ratio	PT ratio	Tissue thrombo-plastin inhibition test ratio	Platelet $\times 10^9$/l	Clinical features and drug history	Bleeding
1	M	64	2.11*	2.15	1.10	1.44	169	Coagulation screening prior to surgery for prostatic adenoma	
2	M	49	1.49	1.42	1.14	1.43	61	Drug-induced thrombocyto-penia (quinidine)	Bruising and haematoma
3	F	26	1.52*	1.40	1.09	1.63	51	Idiopathic thrombocytopenic purpura	–
4	F	59	1.41	1.64	1.00	1.57	121	Coagulation screening prior to total hip replacement	Bruising
5	F	16	1.54	1.30	1.41	1.57	225	Antiepileptic drugs	Bleeding after dental extraction
6	M	30	1.56*	1.62	1.00	1.45	113	Deep-vein thrombosis and pulmonary embolism	–
7	F	30	1.47	1.31	1.18	1.25	105	–	Bleeding after tonsillectomy
8	F	6	1.28	1.25	1.20	1.54	222	–	Bleeding after dental extraction
9	F	26	2.24	1.99	1.02	1.34	198	Coagulation screening prior to elective surgery	Bruising
10	F	32	1.56	1.63	1.10	1.37	120	,,	–
Control (haemophilia A)			2.10	1.18	1.01	1.00			
Normal range			0.85–1.20		0.80–1.15	0.90–1.10	150–400		

The values of APTT, PT and TTIT are expressed as ratios between clotting time of patient and normal plasma.
The corrected APTT was carried out by testing a mixture of equal volumes of patient and reference normal plasma, and values are expressed as ratios between clotting time of such mixtures and normal plasma.
* The APTT was carried out with a commercial reagent (Cephotest Nyegard).

nuclear antibodies in 2 and of the rheumatoid factor in 1. The diagnosis of SLE, therefore, could be ruled out in all the patients.

Table 2 shows other clinical features. There was an excess of females (7/10) and no definite predilection for age, which ranged from 6 to 64 years. 4 patients (nos 1, 4, 9, and 10) showed no significant clinical findings and were referred prior to surgery; no 3 was known to have thrombocytopenic purpura since the age of 18; no 2 was investigated for bruising problems related to moderate thrombocytopenia following treatment with quinidine; no 6 was referred to us because he had developed deep vein thrombosis and pulmonary embolism 6 months before; finally, nos 7 and 8 (mother and daughter) were investigated for a bleeding after minor surgical procedures.

Main laboratory findings. Table 2 shows that the routine APTT exceeded the upper normal limits in all patients. In 3 patients (nos 1, 3, and 6) the LLAC was discovered at a time when the commercial reagent Cephotest was being used as a routine APTT method in the laboratory, whereas the Kaolin-Thrombofax method was employed when the remaining patients were detected. The abnormal APTT was not corrected by normal plasma: in 4 patients (nos 1, 4, 6, and 10) the corrected APTT ratio was higher than that of patient to normal plasma, suggesting that normal plasma enhanced the inhibitory activity of LLAC plasma. The anticoagulant was time-independent, since incubation at 37° C for up to 2 h of mixtures of patient and normal plasma failed to increase the inhibition.

The TTIT exceeded the upper normal limits in all patients and confirmed the diagnosis of LLAC. To rule out the possible influence of intrinsic thromboplastin formation, the test was carried out with the highest dilution of tissue thromboplastin (Simplastin) which failed to prolong the clotting time of a patient with severe haemophilia A (factor VIII $< 1\ \%$). None of the patients had measurable levels of inhibitors directed specifically towards factors VIII or IX. Human brain PT was slightly prolonged in 3 patients, the thrombin time was consistently normal; a mild degree of thrombocytopenia was detected in 4 patients in addition to those already known to carry this abnormality (patients nos 2 and 3).

Sensitivity to LLAC of APTT reagents. Table 3 shows the ratios of patient to reference normal plasma obtained using nine commercial APTT reagents, our routine method and that of the NRLACR. It is evident that not all the reagents have equal sensitivity to LLAC: only the Bio-Merieux APTT gave abnormal results in all 10 patients; Immuno and NRLACR were abnormal in 9; Behringwerke, Hyland and Nygaard in 8; Boehringer and our routine method in 7; Dade and Ortho in 6 and General Diagnostic reagent gave abnormal results in 5 patients only.

Sensitivity to LLAC of PT reagents. Table 4 shows the ratios of patient to reference normal plasma obtained using 5 commercial PT reagents made with rabbit brain (Bio-Merieux, Boehringer, Dade, Ortho and General Diagnostic), a human placenta preparation (Behringwerke), the human brain NRLACR thromboplastin used routinely in our laboratory and a commercial reagent containing ox brain thromboplastin (Thrombotest). The General Diagnostic

TABLE 3
Sensitivity of APTT reagents to LLAC

Patient no	Behring-werke	Bio-Merieux	Boeh-ringer	Dade	General Diag-nostic	Hyland	Immuno	NRLACR	Nygaard	Ortho	Our routine method Kaolin + Thrombo-fax
1	0.97	*1.30*	1.08	1.12	1.09	0.64	1.00	0.86	*2.11*	*1.60*	1.04
2	*1.41*	*1.57*	*1.28*	1.13	1.16	*1.39*	*1.46*	*1.28*	*1.45*	*1.24*	*1.49*
3	1.16	*1.71*	1.14	1.18	1.11	*1.23*	*1.48*	*1.49*	*1.52*	1.06	1.02
4	*1.58*	*1.30*	*1.36*	*1.23*	*1.24*	*1.37*	*1.42*	*1.35*	*1.95*	*1.28*	*1.41*
5	*1.37*	*1.33*	*1.29*	*1.21*	1.18	1.01	*1.21*	*1.23*	*1.32*	*1.54*	*1.21*
6	*1.58*	*1.31*	1.04	1.10	1.01	*1.22*	*1.26*	*1.41*	1.03	1.03	1.04
7	*1.50*	*1.76*	*1.48*	*1.62*	*1.33*	*1.59*	*1.39*	*1.54*	*1.43*	1.03	*1.47*
8	*1.42*	*1.47*	*1.34*	*1.59*	*1.28*	*1.44*	*1.26*	*1.31*	*1.25*	1.01	*1.28*
9	*2.40*	*1.53*	*2.62*	*2.11*	*1.64*	*2.94*	*1.88*	*2.12*	*2.50*	*1.99*	*2.24*
10	*1.44*	*1.20*	*1.82*	*1.26*	*1.25*	*1.39*	*1.32*	*1.31*	1.22	*1.26*	*1.56*
Normal range	0.85–1.19	0.79–1.17	0.87–1.23	0.85–1.20	0.80–1.20	0.78–1.21	0.83–1.18	0.86–1.16	0.85–1.22	0.85–1.22	0.81–1.20

The values are expressed as ratios of patient to reference normal plasma clotting time. The abnormal ratios are written in italics.

TABLE 4

Sensitivity of PT reagents to LLAC

Patient no	NRLACR (human brain)	Boehringer (rabbit brain)	Simplastin (rabbit brain)	Dade (rabbit brain)	Ortho (rabbit brain)	Bio-Merieux (rabbit brain)	Thrombotest (ox brain)	Behringwerke (human placenta)
1	1.10	1.15	*1.43*	*1.70*	1.00	*1.48*	1.04	1.17
2	1.14	0.99	*1.51*	1.04	0.98	1.04	1.08	1.07
3	1.09	1.07	*1.30*	*1.24*	1.02	*1.18*	1.18	*1.27*
4	1.00	1.10	*1.45*	1.10	1.01	1.02	1.18	*1.21*
5	*1.41*	*1.51*	*1.80*	*1.43*	*1.44*	*1.53*	*1.78*	*1.37*
6	1.00	1.02	*1.18*	1.13	1.02	*1.15*	1.14	1.14
7	*1.18*	*1.26*	*1.40*	*1.16*	1.07	*1.21*	1.17	*1.29*
8	*1.20*	1.15	*1.48*	*1.17*	1.12	*1.34*	*1.42*	1.15
9	1.02	0.94	1.07	1.00	0.96	0.95	1.01	1.02
10	1.10	*1.25*	*1.23*	1.14	1.12	*1.15*	1.03	*1.22*
Normal range	0.85–1.15	0.91–1.16	0.79–1.12	0.88–1.14	0.88–1.15	0.91–1.14	0.84–1.21	0.88–1.16

The values are expressed as ratios of patient to reference plasma clotting time.
The abnormal ratios are written in italics.

TABLE 5

Assays of coagulation factors in LLAC

Patient no	Factor II	Factor V	Factor VII	Factor VIII	Factor IX	Factor X	Factor XI	Factor XII
1	94	111	*72*	*3*	*3*	*57*	118	107
2	101	122	*64*	*20*	*36*	125	128	160
3	82	136	73	*40*	78	*61*	99	69
4	104	109	138	n.p.	n.p.	80	136	134
5	119	67	*30*	*52*	142	*71*	62	61
6	89	80	112	116	105	136	115	64
7	88	64	70	62	70	*63*	115	103
8	119	73	*72*	100	90	91	129	89
9	170	107	87	n.p.	n.p.	83	n.p.	104
10	78	129	128	*12*	n.p.	83	54	67
Normal range	77–132	47–153	73–145	56–148	67–158	72–142	52–148	56–151

The value are expressed in % of reference normal plasma. The abnormal results are written in italics.
n.p. indicates assays giving non-parallel dose response curves.

thromboplastin (Simplastin) gave abnormal results in 9 patients; Bio-Merieux in 7; Dade and Behringwerke in 5; NRLACR thromboplastin and Boehringer in 3; Thrombotest in 2 and Ortho in 1.

Clotting factors in LLAC. The specific one-stage assays of factors II, V and XII gave parellel dose response curves and normal values in all the patients; factors VII and X were slightly decreased in 4 patients. Factor IX was significantly reduced in 2 patients. The most striking abnormalities were found with the one-stage factor VIII assay: at low dilutions (1:3–1:6) of test plasma, 5 patients (nos 1, 2, 3, 5, and 10) gave very low or unmeasurable values which increased at higher dilutions (1:12–1:24) but remained well below the normal range. In 2 patients (nos 4 and 9) non-parallel dose response curves and highly prolonged clotting times were obtained at all the dilutions. This phenomenon was also observed with factor IX assay in these patients and in patient no 10; and with factor XI assay in patient no 9.

DISCUSSION

This study confirms that lupus-like anticoagulants can occur in patients without clinical and laboratory evidence of SLE. 2 patients, however, had autoimmune and drug-induced thrombocytopenia respectively; they also showed antinuclear antibodies, and a further patient was positive for the rheumatoid factor. Hence, development of LLAC in patients without SLE may be related to a background of a disordered immunity, and perhaps more overt immune disease might become apparent during a long-term follow up. The familial occurrence of LLAC, which was not previously reported, suggests that such abnormal immunological reactivity might be genetically determined.

Unlike the majority of previously reported cases (see the reviews of Green 1972, Lechner 1974 and Feinstein & Rapaport 1974) 5 of our patients showed a slight but definite haemorrhagic tendency. If the easy bruisability shown by 2 of them might be related to accompanying mild thrombocytopenia, the post-surgical bleeding observed in the 3 remaining patients cannot be accounted for by this abnormality. Since the anticoagulant seems to interfere with the activation of prothrombin by the prothrombinase complex (Xa, V, Ca^{2+}, phospholipids) (Margolius et al 1961, Feinstein & Rapaport 1972, Lechner 1974), it is not surprising that an inhibitory effect at the junction of intrinsic and extrinsic clotting pathways may lead to an impaired haemostasis.

Detection of LLAC is highly dependent upon the characteristics of the reagents employed in coagulation screening tests. Only one APTT reagent detected the abnormality in all instances. The source of the platelet substitute and the nature of the contact phase activator are unlikely to determine such varied sensitivity, because rabbit partial thromboplastin and particulate activator were common features of both the most and least sensitive reagents (Bio-Merieux and General Diagnostic, respectively). Partial thromboplastins of human origin (NRLACR and Behringwerke) were not superior to those of animal origin. Sensitivity of a given method might perhaps be related to critical concentration of the platelet substitute contained in the APTT. This assumption is supported by the recent observation of Exner et al (1978) that the APTT is rendered more sensitive to the anticoagulant by omitting the plate-

let substitute.

Our findings confirm that the tissue thromboplastin inhibition test is an useful and sensitive screening method (Schleider et al 1976). Since the LLAC abnormality could be detected in 9 out of 10 patients using undiluted Simplastin in a conventional prothrombin time, such usefulness might be simply related to the use of this particular tissue thromboplastin made more sensitive by dilution. Influence on the test of intrinsic thromboplastin formation is unlikely, since the clotting time of haemophilic plasma was not prolonged in the experimental conditions adopted in this study. Human tissue thromboplastin was not more sensitive to LLAC than animal material. The presence of LLAC is known to render difficult the one-stage assays of clotting factors, because the anticoagulant interferes with the enzymatic reactions involved in the assay systems and delays the appearance of the fibrin end-point (Corrigan et al 1970, Feinstein & Rapaport 1972, Nilsson et al 1975, Lechner 1974). While factors II, V and XII were normal in all the patients, assays of factors VIII–IX and, to a lesser extent, factors VII, X and XI were characteristic of the presence of an anticoagulant; they showed decreased activity or non-parallel curves at low plasma dilutions which was corrected at higher dilutions. In a few cases, however, low levels of factors VII, VIII, IX, X and XI were also found when test plasma was assayed at dilutions 4 times higher than those of the reference plasma. Specific inhibitors against factors VIII and IX could be ruled out by specific assays, and by the non-progressive nature of LLAC inhibition. Thus, no clear explanation of this phenomenon is presently available. It is possible that LLAC may be directed towards a component of the coagulation pathway acting earlier than the prothrombin activating complex in the coagulation sequence, though it remains unexplained why this does not occur with factor XII measured using the same assay systems.

In conclusion, the fortuitous observation of 9 cases during routine coagulation screening suggests that LLAC is not exceedingly rare, and awareness of this possibility should be kept in mind for an unexplained prolongation of APTT and PT. The detection of LLAC is not only of theoretical interest, but has some clinical implications too because the anticoagulant may be accompanied by a mild bleeding tendency.

REFERENCES

American Rheumatism Association Section of the Arthritis Foundation (1973) In G P Rodnan (ed) *Primer on the rheumatic diseases*, pp 139–47.

Corrigan J, Patterson J H & May N E (1970) Incoagulability of the blood in systemic lupus erythematosus. *Am J Dis Child* **119**, 365–69.

Denson K W E (1972) In Rosemary Biggs (ed) *Blood coagulation, hemostasis and thrombosis*, p 278. Blackwell Scientific Publication, Oxford.

Exner T, Rickard K A & Kronenberg H (1978) A sensitive test demonstrating lupus anticoagulant and its behavioural patterns. *Br J Haematol* **40**, 143–51.

Feinstein D I & Rapaport S I (1972) Acquired inhibitors of blood coagulation. *Prog Hemostasis Thromb* **1**, 75–95.

Feinstein D I & Rapaport S I (1974) Anticoagulants in systemic erythematosus. In E L Dubois (ed) *Lupus erythematosus*, Suppl 2, pp 438–43. University of California Press, Los Angeles.

Green D (1972) Circulating anticoagulants. *Med Clin North Am* **56**, 145–51.

Lechner K (1974) Acquired inhibitors in nonhemophilic patients. *Haemostasis* **3**, 65–93.

Mannucci P M, Pareti F I, Holmberg L. Nilsson I M & Ruggeri Z M (1970) Studies on the prolonged bleeding time in von Willebrand's disease. *J Lab Clin Med* **88**, 662–72.

Margolius A, Jackson D P & Ratnoff O D (1961) Circulating anticoagulants: A study of 40 cases and a review of the literature. *Medicine* (Baltimore) **40**, 145–202.

Nilsson I M, Astedt B, Hedner U & Berezin D (1975) Intrauterine death and circulating anticoagulant ('antithromboplastin'). *Acta Med Scand* **197**, 153–59.

Refsum N, Collen I D, Godal H C, Janson T, Mannucci P M, Nilsson I M & Gilhuus Moe C C (1978) Sensitivity and precision of activated partial thromboplastin time (APTT) methods. A multicenter study. *Scand J Haematol* **20**, 89–95.

Ruggeri Z M (1977) Problems of factor VIII inhibitor assays. In *Workshop on inhibitors of factors VIII and IX*, p 26. Facultas Verlag, Vienna.

Schleider M A, Nachman R L, Jaffe E A & Coleman M (1976) A clinical study of the lupus anticoagulant. *Blood* **48**, 499–509.