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THE LUPUS ANTICOAGULANT-ANTICARDIOLIPIN ANTIBODY SYNDROME

INTRODUCTION

In recent years, studies of the presence of autoantibodies in a variety of disease entities have turned into a voyage of discovery of the possible pathogenic roles that any of the particular specificities may have on the generation of tissue injury. Thus, the primary role of autoantibodies directed against hormone receptors, for example, has clarified the pathogenesis of myastenia gravis, Graves disease, some types of insulin resistance, and pernicious anemia, to name a few. In these grand rounds, we will review the available information dealing with the recently described association between the presence of autoantibodies directed against anionic phospholipids and a constellation of clinical manifestations characterized by high frequency of arterial and venous thrombosis, recurrent abortions, and thrombocytopenia.

BIOLOGIC FALSE-POSITIVE TEST FOR SYPHILIS

With the institution of mass blood testing for syphilis, and the development of specific tests for treponemal antibody, it became apparent in the 1940's that the frequency of biologic false-positive tests (BFP) was considerably higher than it was previously thought to be. Moore and Mohr (1) suggested that among white persons of relatively high socio-economic status, at least half of the seropositive tests found by routine blood testing were BFP reactors.

Serial testing of reactors indicated that these can be separated into two groups: the "acute" and "chronic". The "acute" reactors show positive tests transiently; reversion to seronegativity may be seen within days or weeks. This pattern is associated with any one of several nonsyphilitic acute infectious diseases, as shown in Table 1. The only exception in this group is that of leprosy which is known to be associated with "chronic" BFP reactions.

The incidence of "chronic" BFP reactions in the general population is variable. When "chronic" BFP reactions are defined as those showing at least two positive tests for 6 months or more, approximately 1% of white individuals of upper socioeconomic status were positive (2-4). Table 1 shows a partial list of conditions associated with chronic BFP reactions. It is apparent that among the group of patients without overt infectious processes patients with systemic lupus erythematosus have a significant prevalence of chronic BFP reactions.

TABLE 1

PREVALENCE OF BIOLOGIC FALSE-POSITIVE REACTIONS

INFECTION	DISEASE CONDITION	PERCENT
BACTERIAL	LEPROSY	24
	CHANCROID	5
	SCARLATINA	5
	TUBERCULOSIS	3-5
	PNEUMOCOCCAL PNEUMONIA	2-5
SPIROCHETAL		
	RELAPSING FEVER	30
	RAT-BITE FEVER	20
	LEPTOSPIROSIS	10
PLASMODIAL		
	MALARIA	11
RICKETTSIAL		
	TYPHUS	20
PROTOZOAL		
	TRYPANOSOMIASIS	10
VIRAL	VACCINIA	2
	LYMPHOGRANULOMA VENEREUM	20
	HEPATITIS	10
	MEASLES	5
	RUBELLA	5
	AIDS	
NONE	SYSTEMIC LUPUS ERYTHEMATOSUS	20-30
	RHEUMATOID ARTHRITIS	0-5
	ELDERLY (FEMALES)	6

Modified from Moore and Mohr (1)

The occurrence of positive serologic tests for syphilis in SLE has been recognized for over 60 years, and some workers believed that the two diseases were related etiologically (5). Even before the advent of more specific tests for syphilis, it was apparent that many SLE patients had no history of exposure to the spirochete. The antibody titers were low, and there were marked fluctuations in the tests results from week to week (6). The prevalence of BFP reactions in patients with SLE has varied widely between series (7). This variability is probably due to the heterogeneity of the patient populations tested, because the reagin titers correlate with disease activity, and the tests may become negative in patients undergoing spontaneous or therapeutic remissions.

The frequency of BFP reactors in other connective tissue diseases is low. In discoid lupus, BFP reactors make less than 5% of the patients (8,9). In a large series of patients with rheumatoid arthritis and ankylosing spondylitis, Salo et al. (10) reported a prevalence of less than 0.1% positive tests.

Of particular interest are the studies dealing with the clinical associations found in surveys of individuals with BFP reactions in the general population.

TABLE 2

CLINICAL SIGNIFICANCE OF BFP REACTIONS IN LARGE POPULATIONS

	PERCENT
FEMALE	66
SLE	10-40
"SYSTEMIC" DISEASE	20-40
LABORATORY ABNORMALITIES	70
NORMAL	25

In general, two-thirds of the BFP reactors are female, and within this group, the incidence of SLE appears to be much higher than in males (11-12). In a series from Finland (12), SLE was found in 14 of 65 females and in only one of 16 males. In individuals without overt clinical manifestations, the incidence of laboratory abnormalities is very high (13,14). These include polyclonal gammopathy, positive antinuclear, rheumatoid factor, and Coombs tests. Of particular importance, are the studies dealing with long-term follow-up of asymptomatic BFP reactors (7,11,12). There is general agreement that this group, particularly females, have a high propensity, close to 50 percent, to develop SLE which in some cases emerges 10 years after the discovery of the positive BFP reactions.

ANTICARDIOLIPIN ANTIBODIES

Several observations regarding the specificity of abnormal antibodies present in patients with SLE suggested that a family of these autoantibodies may react with phospholipid antigens. 1) The substrate used in the serologic tests for syphilis is a mixture of cholesterol, phophatidyl choline, and cardiolipin, 2) some anti-DNA antibodies are known to react with the phospholipid backbone of the DNA molecule (15), and 3) lupus anticoagulants have been associated with the presence of phospholipid antibodies.

ANTIPHOSPHOLIPID ANTIBODIES

BIOLOGIC FALSE-POSITIVE TESTS FOR SYPHILIS
ANTICARDIOLIPIN ANTIBODIES
ANTI-DNA ANTIBODIES
LUPUS ANTICOAGULANTS

For these reasons, Harris et al (16) in 1983 developed a radioimmunoassay using cardiolipin as the antigen to detect antibodies in the serum of BFP reactors with SLE. These authors found that the immunoassay was 200-400 fold more sensitive than the VDRL precipitation test. They studied 59 patients with SLE, 3 with mixed connective tissue disease, 2 with vasculitis, and 1 with Sjögren's syndrome. Of these 65 patients, 12 (18%) had positive VDRL tests. Forty of the sixty five patients studied (61%) had raised anticardiolipin levels of at least one immunoglobulin class; 54% had IgG anticardiolipin, and 41% had IgM antibodies.

Table I Thyroid Cancer Death Rates and Prevalence of Occult Thyroid Cancer in Three Populations

	Thyroid Cancer Death Rates/ 100,000/Year		Occult Thyroid Cancer
	Men	Women	%
Switzerland	1.51	1.56	1.2
United States	0.4	0.8	5.7
Japan	0.21	0.46	17.9

(From Ref. 7)

Since the biological risk of this occult minimal papillary carcinoma is probably negligible, these tumors rarely are a cause of death. Such tumors are responsible for the disparity between thyroid cancer as a cause of death and thyroid cancer prevalence. Since the overall annual U.S. death rate from thyroid cancer is about 0.5 per 100,000 population, deaths from thyroid cancer are uncommon compared with deaths from other cancers. The presence of occult tumors of little biological significance detected at operation makes it difficult to discuss incidence. The Third National Cancer Survey reported an age adjusted incidence of thyroid cancer at approximately 0.004% per year for the general population or 40 cases per million persons (8). Expressed in the same terms the average 4% prevalence of thyroid nodules is 40,000 per million persons.

Since most patients with any mass detected in the thyroid might be concerned about malignancy, an initial consideration must be whether the common nontoxic multinodular goiter is associated with increased likelihood of thyroid cancer. As discussed in detail by Burrow, examination of the question from several perspectives does not support an increased risk of cancer in nontoxic multinodular goiters (9). In contrast there is general agreement that there is an increased risk of thyroid cancer in solitary thyroid nodules (6, 10, 11). The frequency of cancer in such nodules is not reliable in most surgical reports because of selection bias. The best estimate for patients who come to medical attention because of a solitary thyroid nodule is probably a 5 to 10% frequency of cancer (6, 10, 11). However, one must keep in mind that in most surgical series an occult cancer found in the thyroid lobe resected but distant from the palpated nodule will be reported as a cancer found.

6. Silverberg SG, Vidone RA: Carcinoma of the thyroid in surgical and postmortem material. Analysis of 300 cases at autopsy and literature review. Ann Surg 164:291-299, 1966.

7. Sampson RJ: Prevalence and significance of occult thyroid cancer. In: Radiation-associated thyroid carcinoma. LJ DeGroot, LA Frohman, EL Kaplan, S Refetoff (eds). Grune and Stratton, New York, pp 137-153, 1977.

The lupus anticoagulant was detected in 49% of the 65 patients studied. Of these 32 positive patients, 91% had raised anticardiolipin levels of at least one immunoglobulin class confirming the close correlation between anticardiolipin and the lupus anticoagulant.

Subsequent studies confirmed the increased frequency of anticardiolipin antibodies in SLE and in a variety of related and unrelated diseases. However, the results have varied widely between studies due to a technical factors such as the nature of the antigen, and wether it is used in suspension or adherent to a surface, which immunoglobulin class or subclass is analyzed; the temperature and pH of the reaction mixture; and the concentration of divalent cations.

TABLE 3

FREQUENCY OF CARDIOLIPIN ANTIBODIES IN SLE

NO OF PATIENTS	PERCENT POSITIVE	REFERENCE
65	61.0	16
55	23.6	16
24	41.7	18
51	49.0	19
65	29.2	20
86	20.9	21

The autoantibodies have also been detected in a variety of diseases of which a partial list is shown in Table 4.

In most studies including non-selected cases, the presence of anticardiolipin antibody was not associated with increased incidence of thrombotic episodes or recurrent abortions. This is probably due to the use of a common laboratory abnormality (anticardiolipin) to calculate probabilities of association with rare events. When the patients are selected on the basis of a previous history of thrombosis or recurrent abortions, then the association with anticardiolipin antibodies becomes apparent. We will explore this area more thoroughly after discussing the clinical implications of the lupus anticoagulant.

TABLE 4

DISEASES WITH ASSOCIATED ANTICARDIOLIPIN ANTIBODIES

DISEASE	REFERENCE
SYSTEMIC LUPUS ERYTHEMATOSUS	16,18,19,20,21
RHEUMATOID ARTHRITIS	22,23
PSORIATIC ARTHRITIS	22
SCLERODERMA	21
MIXED CONNECTIVE TISSUE DISEASE	21
SJÖGREN'S SYNDROME	21
DERMATOMYOSITIS	21
BEHÇET'S SYNDROME	24
DEGÖS' DISEASE	25

LUPUS ANTICOAGULANT

Lupus anticoagulant activity in two patients with SLE was first reported by Conley and Hartmann in 1952 (26). These patients had a prolonged whole blood clotting time, prothrombin time, and evidence of plasma anticoagulant activity. It soon became apparent that this group of patients rarely showed evidence of a bleeding diathesis. On the contrary, the patients with lupus anticoagulant appeared to have higher incidence of venous and arterial thrombosis. This was first recognized by Bowie et al in 1963 (23) who described 4 patients with SLE, thrombosis and lupus anticoagulant. This clinical association has been amply confirmed by many investigators, but as previously described in the case of the anticardiolipin antibodies, there are many more patients with lupus anticoagulant than with thrombotic episodes. In SLE, the reported prevalence of lupus anticoagulant has varied widely between 6% (28,29) to 71% (30) in randomly selected patients. This variability is due to the lack of standardization of the tests to detect the factor, and the poor reproducibility of any given test.

Lupus anticoagulants are immunoglobulins that interfere with phospholipid-dependent clotting tests. Positive plasmas usually show prolonged activated partial thromboplastin times (aPTT) and no correction with 1:1 mixing with normal plasma. Thus, the concentration of phospholipid in the substrates used to measure the aPTT determines the sensitivity of the test. Moreover, contamination with platelet-derived phospholipids in the plasmas to be tested also influence detection of lupus anticoagulants. The most sensitive test appears to be the one where no exogenous phospholipid is used, such as the kaolin clotting time (30).

When retrospective analysis of large numbers of patients with lupus anticoagulants is done, it is clear that only about 50% of these patients meet the criteria for the diagnosis of SLE (31,32). The other 50% may have lupus-like diseases not fulfilling the criteria for the diagnosis of SLE; patients presenting with isolated episodes of venous or arterial thrombosis; patients with repeated abortions; patients on certain drugs, such as procainamide or phenothiazines; children with recent viral infections, and patients without bleeding or clotting abnormalities with the lupus anticoagulant as an incidental finding.

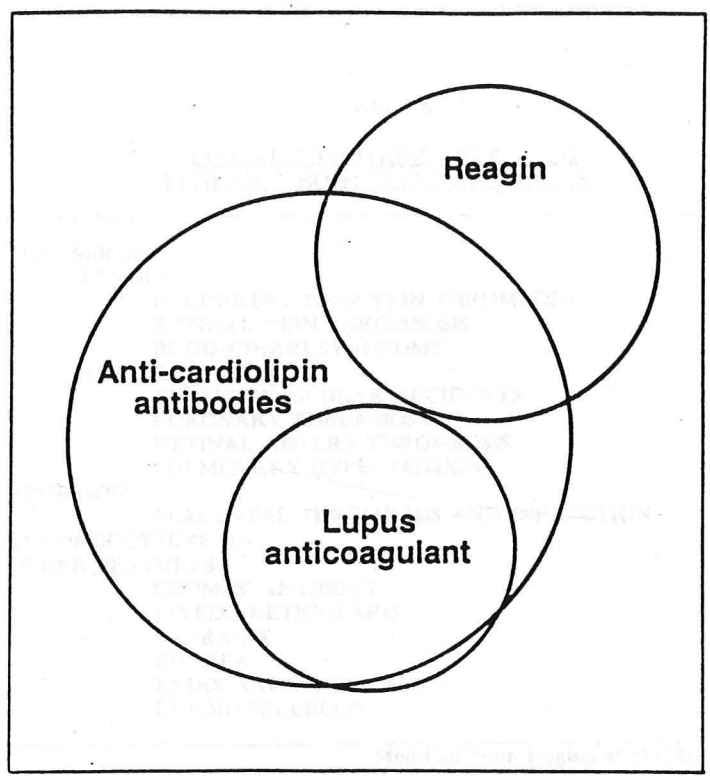
TABLE 5

LUPUS ANTICOAGULANT: DISEASE ASSOCIATIONS

SYSTEMIC LUPUS ERYTHEMATOSUS
LUPUS-LIKE DISEASES
PROCAINAMIDE-PHENOTHIAZINE-INDUCED
ISOLATED THROMBOTIC EVENTS
RECURRENT ABORTIONS
ACUTE VIRAL INFECTIONS
INCIDENTAL FINDING

Thus, the three autoantibodies discussed: BFP factors, anticardiolipin antibodies, and lupus anticoagulants belong to the family of antiphospholipid antibodies. Early studies had shown that lupus anticoagulants were often detected in patients with SLE and BFP reactions (26,33,34). The studies of Harris et al (16) discussed above also showed an excellent correlation between the presence of anticardiolipin antibodies, lupus anticoagulants, and BFP reactions. The exact relationship between these three groups of antibodies remains to be determined. There is abundant evidence to suggest that the antibodies responsible for the lupus anticoagulant make up a subset of patients with anticardiolipin antibodies (16,35). Several studies, however, have failed to confirm a correlation between VDRL titers in patients with syphilis and anticardiolipin antibody levels (18,36). Immunologic studies suggest that the antibodies responsible for the VDRL reaction in patients with syphilis may bind preferentially to antigenic determinants in cardiolipin incorporated into liposomes, whereas the anticardiolipin antibodies in autoimmune states react preferentially with this phospholipid bound to a solid surface (37).

HYPOTHETICAL RELATIONSHIP BETWEEN PHOSPHOLIPID ANTIBODIES



CLINICAL CORRELATIONS

A variety of clinical manifestations have been associated with antiphospholipid antibodies. Table 6 shows a list of the most common conditions reported.

TABLE 6

CLINICAL CONDITIONS ASSOCIATED WITH ANTIPHOSPHOLIPID ANTIBODIES

1.	THROMBOSIS	
	VENOUS	
		RECURRENT DEEP VEIN THROMBOSIS
		RETINAL VEIN THROMBOSIS
		BUDD-CHIARI SYNDROME
	ARTERIAL	
		CEREBROVASCULAR ACCIDENTS
		CORONARY THROMBOSIS
		RETINAL ARTERY THROMBOSIS
		PULMONARY HYPERTENSION
2.	ABORTION	
		PLACENTAL THROMBOSIS AND INFARCTION
3.	THROMBOCYTOPENIA	
4.	OTHER FEATURES	
		COOMBS' ANTIBODY
		LIVEDO RETICULARIS
		MIGRAINE
		CHOREA
		ENDOCARDIAL DISEASE
		LUPOID SCLEROSIS

Modified from Hughes et al (38)

1. THROMBOSIS

The best documented clinical manifestation associated with antiphospholipid antibodies is that of venous thrombosis. After the first report of Bowie et al (27) many other studies confirmed the association.

TABLE 7

PREVALENCE OF THROMBOSIS IN PATIENTS WITH LUPUS ANTICOAGULANT

No. of Patients				
Total	With Thrombosis	Without thrombosis	Percent	Reference
8	4	4	50.0	27
8	1	7	12.5	39
12	3	9	25.0	40
35	8	27	22.9	41
6	1	5	16.7	42
14	2	12	14.3	43
7	1	6	14.3	44
19	3	16	15.8	45
31	18	13	58.0	46
35	19	16	54.3	47
84	25	59	29.8	48
259	85	174	32.8	

Modified from Lechner et al (48)

A compilation of 259 patients with lupus anticoagulant from 11 separate studies suggest that the prevalence of thrombotic events in these patietns approaches 30 percent. It is most likely, however, that this figure is a gross overestimation since many patients were tested for the anticoagulant after they presented with a thrombotic event, and conversely many asymptomatic patients with anticoagulant remain undetected. In addition, the prevalence of lupus anticoagulant in unselected patients with thrombotic events is also low. In a series of 800 patients with venous thrombotic disease, only 16 patients with lupus anticoagulant were detected (48).

Over 60 percent of the patients with this constellation present with deep vein thrombosis, often recurrent. Pulmonary embolism is not uncommon; in one series (48) 64 percent of the patients with recurrent deep vein thrombosis had evidence of pulmonary embolization. Thrombotic events are not limited to the peripheral veins. Thrombosis of the renal veins with or without involvement of the inferior vena cava (49), of the hepatic veins with production of Budd-Chiari syndrome (50), and even retinal vein thrombosis (51) have been reported. It is of interest that most of the thrombotic events were spontaneous, and were not related to surgery, trauma, or myocardial infarction.

Asherson et al (52) first reported the association of pulmonary hypertension and lupus anticoagulant in SLE patients without overt thromboembolic disease. They postulated that thrombosis in situ may be occurring in the pulmonary vasculature. In addition, a small group of SLE patients, and a few patients with no evidence of autoimmune disease, with pulmonary hypertension associated with repeated pulmonary embolism have been reported.

Arterial thrombosis occur in about 30 percent of the patients with anticoagulant and clotting events (48). In general, thrombosis of the cerebral arteries is more common than occlusive disease of the peripheral arteries. The central nervous tissue manifestations associated with antiphospholipid antibodies will be discussed in the next section. Involvement of large arteries is not unusual. Isolated cases have been reported with gangrene following occlusion of peripheral vessels (54), mesenteric thrombosis with bowel infarction (55), aortic arch syndrome (56) with "pulseless disease", and even occlusion of the aorta itself (57). Characteristically, histologic examination of the affected vessels shows no evidence of vasculitis (58).

TABLE 8

ARTERIO-OCCLUSIVE MANIFESTATIONS IN PATIENTS WITH ANTIPHOSPHOLIPID ANTIBODIES

PERIPHERAL GANGRENE
BOWEL INFARCTION
AORTIC-ARCH SYNDROME
AORTIC OCCLUSION
RENAL INFARCTION
GLOMERULAR THROMBOSIS
CORONARY OCCLUSION IN YOUNGER PATIENTS
RETINAL ARTERY THROMBOSIS

The renal vessels are also involved in patients with lupus anticoagulant. In a study of 105 renal biopsies from 71 patients with SLE, Kant et al (59) found a high correlation between the presence of glomerular-capillary thrombosis in the absence of necrosis and the lupus anticoagulant. Lupus anticoagulant was present in 6 of 14 biopsies showing glomerular thrombosis and absent in 69 of 71 biopsies of patients without lupus anticoagulant ($p<0.001$).

TABLE 9

RELATIONSHIP BETWEEN LUPUS ANTICOAGULANT AND GLOMERULAR THROMBOSIS

THROMBOSIS	LUPUS ANTICOAGULANT		
	PRESENT	ABSENT	TOTAL
PRESENT	6	8	14
ABSENT	2	69	71

Modified from Kant et al (59)

Of particular interest are the reports demonstrating an increased incidence of coronary occlusive disease in surviving patients younger than 45 years old (60-62). These patients had no evidence of generalized coronary-artery disease, and did not show risk-factor profiles different from those of the controls. In a recent study by Hamster et al. (62), 21 percent of 62 such patients had raised anticardiolipin antibody levels. Eight of the 13 patients with antibodies, and only 12 of 49 with no antibodies had major cardiovascular events subsequently ($p<0.05$). Two patients with cardiolipin antibodies developed cerebral infarction; 2 with arterial occlusion of the lower limb; 2 with new myocardial infartion; 1 with pulmonary embolism; and 1 with deep vein thrombosis. The eight affected patients had cardiolipin antibody titers 5 times over the mean for normal blood donors. These authors concluded that "antibodies to cardiolipin are common in young post-infarction patients and should be interpreted as markers of high risk for recurrent cardiovascular events" (62).

CENTRAL NERVOUS SYSTEM MANIFESTATIONS

Many reports of small series and isolated cases of neurologic diseases associated with the lupus anticoagulant or anticardiolipin antibodies have appeared in recent years (63).

TABLE 10

NEUROLOGIC DISEASE IN ASSOCIATION WITH ANTIPHOSPHOLIPID ANTIBODIES

FOCAL CEREBRAL ISCHEMIA
TRANSIENT ISCHEMIC ATTACKS
ISCHEMIC INFARCTION
MULTI-INFARCT DEMENTIA
CEREBRAL VENOUS THROMBOSIS
OCULAR ISCHEMIA
AMAUROSIS FUGAX
RETINAL VEIN THROMBOSIS
RETINAL ARTERY THROMBOSIS
CHOROIDAL INFARCTION
MYELOPATHY
LUPOID SCLEROSIS
JAMAICAN NEUROPATHY
DEGOS' DISEASE
GUILLAIN-BARRÉ SYNDROME
MIGRAINE
CHOREA
SNEDDON'S SYNDROME

Modified from Levine and Welch (63)

As discussed previously, in a significant proportion of patients with antiphospholipid antibodies and arterial thrombosis, the disease frequently involves the cerebral vessels. This association is therefore of particular clinical interest in patients with SLE, where CNS manifestations and lupus anticoagulants are common. In a study by Harris et al. (64) of 15 SLE patients with cerebral thrombosis, 13 had high titers of anticardiolipin antibodies. The cerebrovascular accidents were often multiple and severe, and they occurred in patients with no evidence of active lupus. In a small group of SLE patients with recurrent strokes and multi-infarct dementia vasomotor manifestations such as migraine headaches and livedo reticularis were also associated with CNS disease (65).

Certain nonthrombotic syndromes resembling myelopathies have also been associated with antiphospholipid antibodies, suggesting that these may play a direct pathogenic role by crossreacting with cerebral phospholipids. Chorea is a rare but well documented CNS manifestation in patients with SLE. A recent report described a group of 12 patients with lupus and chorea (66). Chorea became apparent early in the course of the disease in most patients. Nine of the 12 patients demonstrated anticardiolipin antibodies, and 7 subsequently developed cerebral infarctions or transient ischemic attacks.

Other neurological manifestations reminiscent of demyelinating processes in patients with anti-phospholipid antibodies include the so called "lupoid sclerosis" syndrome (67,68) and the "Jamaican neuropathy" (69,70), both featuring transverse myelopathy and anticardiolipin antibodies. Fulford et al (67) described six young women with transverse myelopathy, BFP reactions, and positive antinuclear factors. The authors coined the name "lupoid sclerosis" because they felt that these patients were suffering from a variant of multiple sclerosis.

2. OBSTETRIC MANIFESTATIONS

Antiphospholipid antibodies have been associated with a group of obstetric problems featuring primary recurrent abortions and fetal distress (Table 11). The association of recurrent fetal loss with the lupus anticoagulant in patients with SLE was first reported by Nilsson et al in 1975 (71) and subsequently confirmed by many authors (72-77). In many instances, a "decidual vasculopathy" characterized by thrombotic placental infarction has been found (78). In some cases, only a small placenta is found, and in others no evidence of vascular damage has been detected.

TABLE 11

OBSTETRIC MANIFESTATIONS ASSOCIATED WITH ANTIPHOSPHOLIPID ANTIBODIES

RECURRENT ABORTIONS
FETAL DISTRESS
PRE-ECLAMPSIA
POSTPARTUM SYNDROME

The clinical importance of the lupus anticoagulant in pregnant SLE patients is fairly well established, and the high frequency of fetal wastage in this disease is well known. In a prospective study, Lockshin et al (76) found that 9 of 21 SLE patients with a history of recurrent abortions had high levels of anticardiolipin antibodies suggesting that these may be a marker in less than 50 percent of the patients. The role of antiphospholipid antibodies in patients with recurrent abortions but without clinical evidence of SLE is more difficult to assess. Unander et al (79) reported that in a group of 99 patients with unexplained habitual abortions, 42 had increased anticardiolipin levels. In 10 patients with the highest levels, all with primary habitual abortions, there was a concomitant decrease in the serum concentration of the fourth component of complement.

TABLE 12

DISTRIBUTION OF ANTICARDIOLIPIN ANTIBODY LEVELS IN WOMEN WITH HABITUAL ABORTIONS

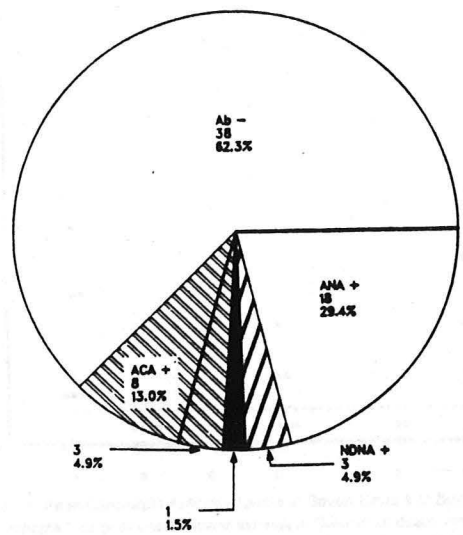
Anticardiolipin antibody Units		No. of patients		
IgG	IgM	Primary Habitual abortion	Secondary Habitual abortion	Total
0-2	0-2	35	22	57
	3-7	5	2	7
3-4	ND*	10	4	14
5-4	ND	7	4	11
>10	ND	10	0	10
Total		67	32	99

*ND=not detected

From Unander et al (79)

A second interesting study by Cowchock et al (80) included 61 patients with unexplained repeated abortions, and 21 with repeated abortions with a known cause as controls. Thirteen percent of the 61 patients showed antibodies to cardiolipin, while none were found in the control group. In addition, 30 percent of the patients exhibited positive antinuclear factor tests, and these made a mostly non-overlapping group with respect to the patients with cardiolipin antibodies. In contradistinction to the previous study, the group of 8 patients with cardiolipin antibodies had secondary abortions.

AUTOANTIBODIES IN PATIENTS WITH UNEXPLAINED REPEATED ABORTIONS



From Cowchock et al (80)

A third controlled, prospective study of 44 consecutive women with idiopathic habitual abortion (81) reported only 9 percent prevalence of lupus anticoagulant, 11 percent for cardiolipin antibodies, and 16 percent for positive antinuclear factor tests. These numbers were not statistically different from those of the control population. However, the mean antibody levels in the aborters were significantly higher than those in control subjects for anti-DNA ($p=0.004$), lupus anticoagulant ($p=0.05$), and anticardiolipin antibody ($p=0.0007$). These findings indicate that although there is a significant association between antiphospholipid antibodies and idiopathic abortion, these may be a marker for a relatively small portion of the population of habitual aborters without SLE.

In a prospective study of pregnancies in women with SLE, Lockshin et al (76) examined the relation between antibody to cardiolipin, and midpregnancy fetal distress, identified by abnormal anti-partum fetal heart-rate or by fetal death. All of 9 SLE patients with evidence of fetal distress showed abnormally high antibody levels. None of 12 pregnant SLE patients without this complication had abnormal antibody

levels. Thus, anticardiolipin antibody appears to be a good predictor of fetal distress or death in SLE patients.

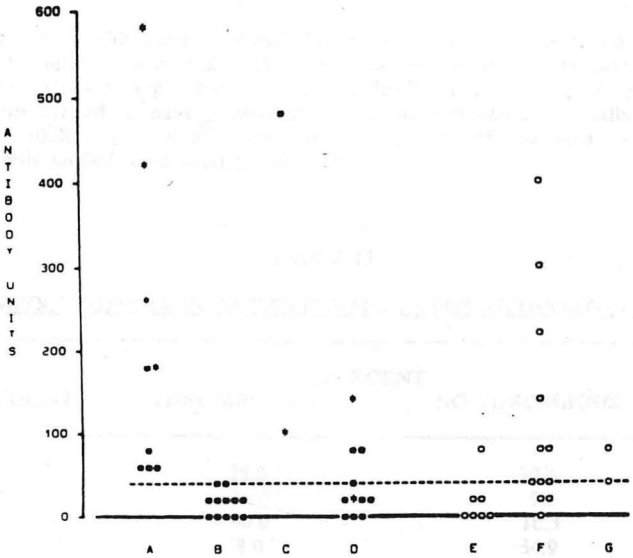


Figure 1. Peak Cardiolipin Antibody Levels in Seven Groups of Subjects.
Asterisks indicate fetal or neonatal (lower asterisk in Column D) death, closed circles women with live-born surviving children, and open circles nonpregnant controls. The dashed line indicates the upper limit of normal (mean +2 S.E.M.). No women with lupus and abnormal fetal heart-rate tests had normal antibody values, and no women with normal fetal heart-rate tests had abnormal values. Fetal death occurred in six of the eight women with values >100 units. A denotes patients with lupus and abnormal fetal heart rates (n = 9, 212.3±55.3 units), B patients with lupus and normal fetal heart rates (n = 12, 27.5±3.4), C pregnant patients with anticoagulant only (n = 2, 297.0±135.1), D pregnant subjects without lupus (n = 12, 42.5±11.0), E normal nonpregnant subjects (n = 7, 28.2±10.1), F nonpregnant subjects with lupus (n = 12, 117.4±35.0), and G patients with syphilis (n = 2, 61.5±7.4). Seven subjects in Group D, including those with fetal or neonatal death, underwent fetal heart-rate testing; only the two indicated by an asterisk had abnormal values. Group A differed from B ($P<0.005$), D, and E ($P<0.01$) but not from F ($P>0.10$). Groups B, D, and E did not differ significantly (two-tailed t-test for differences of means).

From Lockshin et al. (76)

An unusual post partum syndrome in three patients with antiphospholipid antibodies has been described recently (82). These patients developed pulmonary infiltrates, pleural effusions and fever. No evidence of infection or pulmonary embolism was found that could explain the findings. All three patients had electrocardiographic abnormalities, and one developed a cardiomyopathy with immunoglobulin and complement deposition in the myocardium.

3. HEMATOLOGIC ABNORMALITIES

Thrombocytopenia is the most common hematologic disorder associated with the presence of the lupus anticoagulant and anticardiolipin antibodies (83,84). In the series of 84 patients with lupus anticoagulant studied by Lechner et al. (48), patients with thrombosis tended to have a moderately low platelet count, typically between 150,000 and 50,000 per mm^3, whereas the group of patients with severe thrombocytopenia tended to be spared (Table 13).

TABLE 13

THROMBOCYTOPENIA IN PATIENTS WITH LUPUS ANTICOAGULANT

PLATELET COUNT	PERCENT THROMBOSIS	PERCENT NO THROMBOSIS
$>150 \times 10^3$	28.0	39.5
$100\text{-}150 \times 10^3$	24.0	9.3
$50\text{-}100 \times 10^3$	40.0	16.3
$<50 \times 10^3$	8.0	34.9

Modified from Lechner et al. (48)

Correlation with thrombocytopenia has also been noticed in some of the reported series of patients with habitual abortion. Lubbe et al (75) described a group of six patients with a history of repeated abortions and lupus anticoagulant. Three of the six had thrombocytopenia, and in two of the remaining three, the platelet count was borderline low. Similar results were published by Lockshin et al (76) in their group of 21 pregnant patients with SLE. Of the nine patients with lupus anticoagulant and fetal distress or fetal death, five had thrombocytopenia. Only one of the remaining 12 patients with no evidence of cardiolipin antibodies had a low platelet count. Wether or not the antiphospholipid antibodies can bind to platelets will be discussed in the next section.

The association of hemolytic anemia or a positive Coombs' test without overt hemolysis and phospholipid antibodies has also been noted. Tincani et al. (19) found a higher prevalence of positive Coombs' tests in patients with cardiolipin antibodies compared to a cardiolipin-negative group.

MECHANISMS OF ACTION

It should be pointed out that the exact pathogenic role of the family of phospholipid antibodies in the development of the clinical manifestations discussed above has not yet been resolved. It is possible that these autoantibodies are only a marker that identifies a group of patients with the tendency to express blood clotting abnormalities. However, the strong correlation existing between the presence of lupus anticoagulant and phospholipid antibody makes a compelling argument for the possibility that these antibodies could play a direct role in the development of the clinical manifestations described.

TABLE 14

POSSIBLE SITES OF ACTION OF PHOSPHILIPID ANTIBODIES ON THE COAGULATION CASCASE

PLATELETS
ENDOTHELIAL CELLS
PROSTACYCLIN PRODUCTION
PREKALLIKREIN ACTIVITY
PROTEIN C ACTIVATION

The possibility that a subpopulation of antiphospholipid antibodies may be responsible for in vivo platelet activation and/or damage is attractive. We have already mentioned the positive correlation reported by many authors between thrombocytopenia and the lupus anticoagulant. Moreover, addition of platelet phospholipid to plasmas containing lupus anticoagulant usually corrects the prolonged activated thromboplastin time (85). An effect on platelet function would explain the development of arterial thromboses in some patients since platelet abnormalities have been previously associated with arterial disease, whereas other primary deficiences, such as those of anti-thrombin III and protein C, apparently predispose only to venous or microvascular thrombosis. It remains to be demonstrated however, that the same immunoglobulin molecules that interfere with prothrombinase action on prothrombin can actually bind to platelets or modify their function.

A second hypothesis has been put forward based on the possible interactions between the autoantibodies and endothelial cell membrane phospholipids. Carreras et al. (73,86) postulated that the phospholipid antibodies could disrupt the arachidonic acid pathway and inhibit production of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. These authors showed that immunoglobulins obtained from a patient with a history of recurrent arterial thrombosis, repeated abortions, and the lupus anticoagulant reduced the release of prostacyclin from rat aorta or pregnant human myometriun. This inhibitory effect was abolished by addition of arachidonic acid. They also showed that the patients' IgG reduced the production of 6-keto $PGF_{1\alpha}$ by cultured bovine endothelial cells. Carreras et al. hypothesized that the reduction in prostacyclin formation by vessel walls would result in an increase in the aggregability

of circulating platelets, therefore facilitating the development of venous and arterial thrombosis.

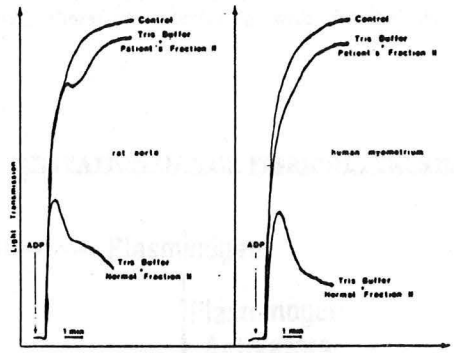


Fig. 1—Inhibitory effect of patient's fraction II on prostacyclin production by a fresh fragment of rat aorta and pregnant human myometrium.

From Carreras et al. (73)

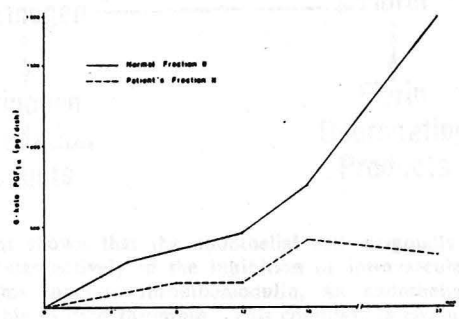


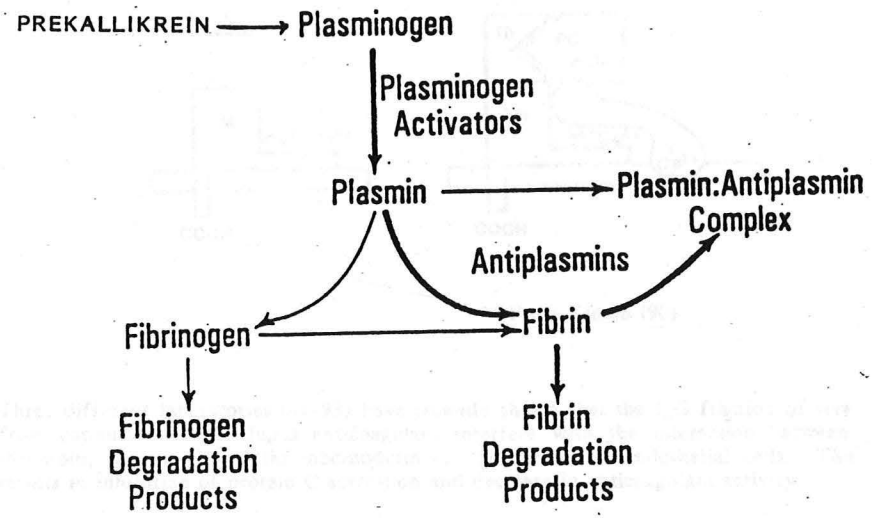
Fig. 2—Inhibitory effect of patient's fraction II on production of 6-keto-$PGF_{1\alpha}$ by cultured bovine endothelial cells incubated in tris buffer.

From Carreras et al (73)

This interesting observation has not yet been tested with a larger number of patients. Moreover, Baguley et al (87) have recently failed to demonstrate significant binding of immunoglobulins to cultured human endothelial cells by the sera of patients with antiphospholipid antibodies. They tested sera from 45 patients, and only 3 demonstrated the presence of antiendothelial antibodies. It should be pointed out that 20 of the 45 patients tested had experienced major thrombosis.

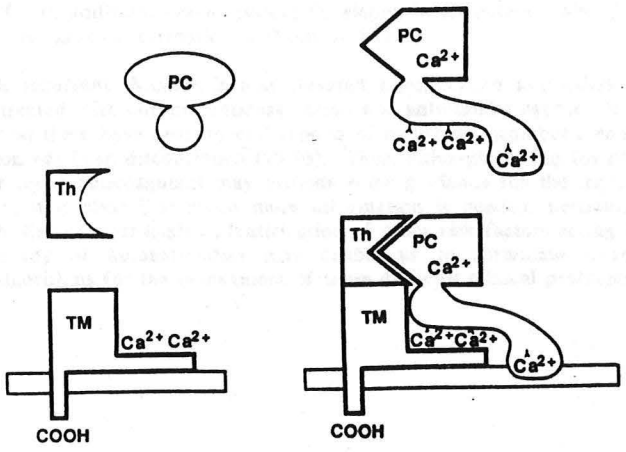
An alternative hypothesis was put forward by Angles-Cano et al. (40) and subsequently confirmed by Sanfellipo and Drayna (88) and Elias and Eldor (89). These workers showed that the sera from several patients with lupus anticoagulant inhibited prekallikrein activity, therefore interfering with fibrinolysis and facilitating clot formation.

ACTIVATION OF THE FIBRINOLYTIC SYSTEM



Recent work has shown that the endothelial cell, originally perceived as a passive surface, participates actively in the inhibition of intravascular coagulation. One of the main systems involves thrombomodulin, an endothelial cell membrane-bound protein that is able to bind thrombin. This complex, in conjunction with phospholipid and Ca++ are potent activators of protein C. Protein C then functions as an anticoagulant by inactivating two of the regulatory proteins of the coagulation pathway, factors Va and VIIIa (90).

PROTEIN C ACTIVATION



From Esmon (90)

Three different laboratories (91-93) have recently shown that the IgG fraction of sera from patients with the lupus anticoagulant interfere with the interaction between thrombin, protein C and thrombomodulin on the surface of endothelial cells. This results in inhibition of protein C activation and decrease in anticoagulant activity.

MANAGEMENT CONSIDERATIONS

From the above discussion it is obvious that the precise mechanisms of action of the phospholipid antibodies have not yet been clarified. However, the clinical correlations described suggest that testing for the presence of lupus anticoagulant or cardiolipin antibodies can provide useful prognostic and therapeutic information. It is clear that screening for these autoantibodies in the general population does not help to single out individuals at risk for the development of future disease except in the case of the fortuitous BFP reaction in young females, which may alert the physician for the possible emergence of SLE. Prospective testing for cardiolipin antibodies may also be indicated in pregnant SLE patients. The data presented suggest that high titers of this autoantibody constitute a definite risk factor for fetal distress and fetal death. The study by Lubbe et al. (75) indicates that preventive treatment may lead to improved pregnancy outcome in this group of patients. Lupus anticoagulant was detected in six pregnant women who had 14 previous episodes of intrauterine deaths. These patients were treated with prednisone 40-60 mg/day, and aspirin 75mg/day. Suppression of

lupus anticoagulant activity was achieved in five patients, all of whom gave birth to live infants. These authors concluded that since treatment can lead to successful pregnancies, it would be important to screen all women with SLE for the presence of lupus anticoagulant. This therapeutic approach, however, is not always successful. Branch et al. (94) have reported fetal death inspite of correction of the abnormal activated PTT. In addition, pre-eclampsia developed in all patients who gave birth to live infants, with growth retardation in 3 out of 5 cases.

Patients with recurrent thrombosis and elevated phospholipid antibodies have been successfully treated with chronic anticoagulation and antiplatelet agents. It should be pointed out that there have been several reports of recurrent thrombotic episodes after anticoagulation has been discontinued (95,96). Thus, although testing for phospholipid antibodies or lupus anticoagulant may provide some guidance for the management of these patients, it is clear that much more information is needed, particularly in the form of controlled clinical trials. Identification of other risk factors acting in concert with this family of autoantibodies may enable us to formulate more efficient therapeutic algorithms for the managment of these difficult clinical problems.

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