

# Antiphospholipid Syndrome Nephropathy in Systemic Lupus Erythematosus

ERIC DAUGAS,\* DOMINIQUE NOCHY,\* DU LE THI HUONG,† PIERRE DUHAUT,†  
HÉLÈNE BEAUFILS,‡ VALÉRIE CAUDWELL,\* JEAN BARIETY,\*  
JEAN-CHARLES PIETTE,† and GARY HILL\*

\*Service d'Anatomie Pathologique, Service de Néphrologie et Institut National de la Santé et de la Recherche Médicale (INSERM) U430, Hôpital Broussais, Paris, France; †Service de Médecine Interne, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; and ‡INSERM U423, Groupe Hospitalier Pitié-Salpêtrière, Paris, France.

**Abstract.** In the course of the antiphospholipid syndrome (APS), the existence of vaso-occlusive lesions capable of affecting numerous organs is now well established. The renal involvement attributable to primary APS, APS nephropathy (APSN), corresponds to vaso-occlusive lesions of the intrarenal vessels, associating side-by-side, acute thromboses with chronic arterial and arteriolar lesions, leading to zones of cortical ischemic atrophy. A retrospective study of 114 lupus patients undergoing renal biopsy was undertaken to determine the following: (1) if APSN can be found in the course of systemic lupus erythematosus (SLE); (2) if certain clinical and biologic factors can permit the prediction of the presence of APSN; and (3) if APSN is a superadded renal morbidity factor in lupus patients. This study shows the following: (1) APSN occurs in SLE (32% of patients with renal biopsies) in addition to, and independently of, lupus nephritis; (2) APSN is

statistically associated with lupus anticoagulant but not with anticardiolipin antibodies; (3) APSN is associated with extrarenal APS, mainly arterial thromboses and obstetrical fetal loss, but not with the venous thromboses of APS; (4) APSN is an independent risk factor, over and above lupus nephritis, that contributes to an elevated prevalence of hypertension, elevated serum creatinine, and increased interstitial fibrosis. Thus, it seems likely that, because of its associations with hypertension, elevated serum creatinine, and increased interstitial fibrosis, APSN may worsen the prognosis in these patients. APSN may also have therapeutic significance in that its recognition should permit a better balance between immunosuppressor and antithrombotic and/or vasoprotective therapy. Finally, this study suggests that APSN should be considered as an element to be included in the classification criteria of APS.

The antiphospholipid syndrome (APS) is defined by the association of arterial and/or venous thromboses or obstetrical fetal loss (repeated miscarriages or fetal death *in utero*) with the presence of antiphospholipid antibodies (APL) recognized as lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL) (1,2). This syndrome may be primary or secondary, particularly in association with systemic lupus erythematosus (SLE). APS is a thrombotic process that may involve all levels of the vascular tree and all organs (3). Although renal involvement is often not prominent, numerous observations nonetheless testify to its implication in the course of APS, in which it may worsen the prognosis (4).

In an earlier retrospective study (5) of 16 patients with primary APS (PAPS) in which the clinical and histologic manifestations could be directly attributed to APS in the absence of other processes, we were able to delineate the clinical

and histologic manifestations of the nephropathy of APS (APSN). APSN is clinically manifest by a syndrome of vascular nephropathy, associating hypertension, acute and/or chronic renal insufficiency, and low-grade proteinuria. Histologically, APSN is a vaso-occlusive process associating, side-by-side, acute thromboses (thrombotic microangiopathy [TMA]) and chronic vascular lesions (arterial fibrous intimal hyperplasia [FIH]), arteriosclerosis, and organized thromboses, with or without recanalization. These progress to fibrous occlusion of the involved vessels and lead to the development of zones of subcapsular ischemic cortical atrophy (FCA) in the regions served by these vessels.

On the basis of these results, we have performed a second retrospective study in an attempt to determine: (1) if APSN as we have described it can be found in the most frequent secondary form of APS, which is associated with systemic lupus erythematosus (SLE-APS); (2) if some patients with SLE have risk factors associated with the development of an APSN; and (3) if APSN is a superadded renal morbidity factor in lupus patients.

## Materials and Methods

### Patients

This study included 114 patients followed in the Service of Nephrology of the Hôpital Broussais (Paris, France) and the Service of Internal Medicine of the Groupe Hospitalier Pitié-Salpêtrière (Paris,

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Correspondence to Drs. Eric Daugas and Dominique Nochy, Service d'anatomopathologie, Hôpital Européen Georges Pompidou, 20 rue Leblanc, F-75908 Paris Cedex 15, France. Phone: 33-156093886; Fax: 33-156093889; E-mail: daugas@igr.fr

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France) between 1983 and 2000: (1) having at least 4 American Rheumatism Association criteria for SLE (criteria revised in 1982 and 1997) (6,7) before or at the time of the renal biopsy; (2) having a renal biopsy (performed for alteration of renal function and/or proteinuria and/or hematuria); and (3) having repeated examinations for aCL (90 patients) and/or LA (110 patients) before or at the time of the renal biopsy.

Excluded from the study were patients having vascular lesions possibly due to other causes, such as systemic sclerosis, hemolytic uremic syndrome, systemic vasculitis, etc., noncorticosteroid-induced diabetes and/or diabetic nephropathy on histology, and patients having received cyclosporine. No patient had either clinical or morphologic stigmata of malignant hypertension. Not excluded were patients with lesions of hyaline arteriosclerosis and bland intimal fibrous lesions in larger arteries, typical of the arteriosclerosis of aging. These were not infrequently present but easily distinguished from the lesions of APSN to be described below.

### Patient Information

For each patient, the following data were gathered: demographic information, clinical and laboratory data relative to APS and SLE, renal and urinary data, the duration of treatment by corticoids, immunosuppressors, anticoagulants, antiplatelet agents, and antihypertensive medications and the number thereof at the time of the renal biopsy, and the last serum creatinine (SCr) at the end of follow-up. APS is defined by the association of arterial and/or venous thromboses or obstetrical fetal loss (repeated miscarriages or fetal death) with the presence of antiphospholipid antibodies recognized as LA and/or aCL (1,2). The arterial and venous thromboses included involve the large or medium-sized vessels. APL positivity in the absence of these clinical manifestations does not constitute APS. Furthermore, the presence of biopsy-proven intrarenal thrombosis in this study was not *per se* considered as an inclusion criterion for APS, which is contrary to Sapporo criteria for definite APS (2). Patients were considered to be hypertensive with a systolic BP  $\geq 160$  mmHg and/or diastolic BP  $\geq 95$  mmHg and/or if taking antihypertensive medication (including angiotensin-converting enzyme inhibitors and A2 blockade). No patient had malignant hypertension. Each serum specimen studied for aCL was tested for antinuclear and anti-nDNA antibodies and complement levels (C3, C4). The following were also analyzed: hemoglobin, leukocytes, platelet count, SCr, and urine for proteinuria and hematuria.

The following overlapping groups of patients were established:

1. APS: lupus patients with APS (24 patients). Non-APS: lupus patients without APS (83 patients).
2. LA: lupus patients with LA (33 patients). Non-LA: lupus patients without LA (77 patients).
3. aCL: lupus patients with aCL  $\geq 15$  IgG phospholipid (GPL) units (65 patients). Non-aCL: lupus patients with aCL  $< 15$  GPL units (25 patients).
4. APL: lupus patients with aCL  $\geq 15$  GPL units and/or with LA (76 patients). Non-APL: lupus patients without LA and without aCL (20 patients).
5. APS + AT: Patients with arterial thrombosis and aPL (8 patients). Non-APS + AT: patients without the association of arterial thrombosis and aPL (99 patients).
6. APS + VT: patients having a history of large vein thrombosis and/or pulmonary embolism and aPL (10 patients). Non-APS + VT: patients without the association of large vein thrombosis or pulmonary embolism and aPL (97 patients).

7. APS + Obst: patients with at least 3 spontaneous abortions or one fetal death after 12 wk of pregnancy attributed to APS (13 patients). Non-APS + Obst: patients with no history of obstetrical accidents related to APS (80 patients).

The data gathered for the 114 patients being sometimes incomplete, the sum of each group and its control group never equals 114, because of different numbers of patients tested in the different groups. Thus, for example, the sum of APS + non-APS is 107, because in 7 patients only one of the two types of antibodies (aCL or LA) was examined and was negative. Hence the impossibility of categorizing these patients definitely as being APS or non-APS.

The renal biopsies were reviewed by light microscopy. Immunofluorescence data were accepted as initially reported at the time of biopsy. The following histologic data were recorded for each biopsy:

1. Lupus glomerulonephritis and its World Health Organization (WHO) class. For this study, class V was defined as those patients with pure extramembranous lesions without associated proliferative lesions or with only superadded mesangial proliferation (1995 WHO classification [8]). Cases with mixed membranous and proliferative lesions were regarded as class III or IV, according to the percentage of glomeruli involved by the proliferative lesions.
2. Semiquantitative evaluation of the degree of interstitial fibrosis outside of areas of FCA: 0, no fibrosis; 1+,  $< 25\%$  of parenchyma involved; 2+, 25 to 50% of parenchyma; 3+,  $> 50\%$  of parenchyma involved.
3. Lesions suggestive of APSN (as described in reference 5): TMA (with fibrin thrombi in arterioles and glomeruli), FIH (proliferation of myofibroblasts in the intima with reduction of the lumen of small-caliber arteries), organized thrombi with recanalization, fibrous arterial occlusion, and FCA (retracted subcapsular zone of renal parenchyma with fibrous atrophy and/or pseudocystic glomeruli). Simple arteriosclerosis was not included in the lesions suggestive of APSN.

The diagnosis of APSN was made when at least one of the lesions suggestive of APSN was found. Three nonexclusive subgroups (*i.e.*, a patient might belong to more than one group) were formed according to the lesions identified on biopsy:

1. Chronic APSN: FIH and/or organized thrombi and/or fibrous occlusion and/or FCA. Two patients had FIH alone. All other patients with chronic APSN had at least two of these lesions. In this series, no case had FCA alone.
2. Acute APSN: TMA with deposits of fibrin on immunofluorescence (without accompanying immunoglobulins). Nine patients had only acute lesions.
3. FCA: As described above. No case had FCA only.

### Detection of Antiphospholipid Antibodies

aCL (IgG) were determined with standardized enzyme-linked immunosorbent assay commercial kits, and the results were expressed in GPL units. LA were sought using different procedures, such as dilute activated partial prothromboplastin time, kaolin clotting time, diluted prothrombin time, or a combination of these tests. By definition, the studies for aCL had to be  $\geq 15$  GPL units at least two times at  $> 6$  wk intervals for the patient to be included as positive in this study. The same criteria applied for LA positivity. Since 1995, these studies have been performed systematically in all lupus patients followed in our institutions, accounting for 54 patients in this series. Before 1995, the majority of lupus patients had studies for LA, and about two thirds had studies for aCL, accounting for 60 patients in this series.

## Renal Biopsies

Renal biopsies were performed transcutaneously in the absence of contraindications. In patients treated with anticoagulants for thrombotic manifestations of APS and when thrombocytopenia was present, biopsies were performed either by transjugular catheter (21 patients) or surgically (4 patients).

Light microscopic specimens were fixed in alcoholic Bouin solution, paraffin-embedded, and stained with hematoxylin, eosin, and saffran, by periodic acid-Schiff, by Masson trichrome, and by Marizozzi or Jones silver stains.

Immunofluorescence specimens were studied with anti-heavy chain antibodies to IgG, IgA, and IgM, anti-light chain antibodies ( $\kappa$  and  $\lambda$ ), antibodies to complement factors (C1q, C4, and C3), and antifibrinogen (Behringwerke, Marburg, Germany; Dakopatts A/S, Glostrup, Denmark).

## Statistical Analyses

A two-sided  $\chi^2$  test, or a Fisher exact test when required, were performed for all qualitative variables. OR with 95% CI were computed. Quantitative variables were tested for normality, and all were found to be non-normal, so Wilcoxon rank testing was performed for all. Median and extremes are given. In the tests comparing the features of APS (LA, aCL, APS) to APSN, chronic APSN, acute APSN, and FCA, these latter are considered as independent groups to verify their significance. In tests comparing them with the clinical features and particularly with the APS-related manifestations, chronic APSN, acute APSN, and FCA are considered as subgroups of the APSN group.

Finally, multivariate analysis was performed by using a logistic regression model with stepwise selection for all relevant variables associated with the dependent variable at an  $\alpha$ -level  $<0.1$  in univariate analysis. Clinically relevant variables were sometimes included in the logistic regression model even if they were not significantly associated with the dependent variable in univariate analysis (*e.g.*, the WHO class of glomerulonephritis in analyzing the risk factors of hypertension). To use it as a dependent variable, the SCr was converted into a semiquantitative variable: 0,  $\leq 70$   $\mu\text{mol/L}$ ; 1, 71 to 80  $\mu\text{mol/L}$ ; 2, 81 to 90  $\mu\text{mol/L}$ ; 3, 91 to 100  $\mu\text{mol/L}$ ; and 4,  $>101$   $\mu\text{mol/L}$ . The variable for WHO class of lupus nephropathy was defined as follows, roughly in order of ascending severity: 1, class II; 2, class V; 3, class III; and 4, class IV.

## Results

### Patients

This study included 114 patients. Fifteen (13%) were men, 99 (87%) were women, 70.5% were white, 20.5% were black, and 9% were Asian. The median age was 28 yr (13 to 63 yr) at the time of biopsy.

All save two patients (one case of glomerular TMA and one case of glomerular sclerosis without IgG deposits on immunofluorescence) showed lupus glomerulopathy: 18 (16%) WHO class II, 17 (15%) class III, 60 (53%) class IV, and 17 (15%) class V.

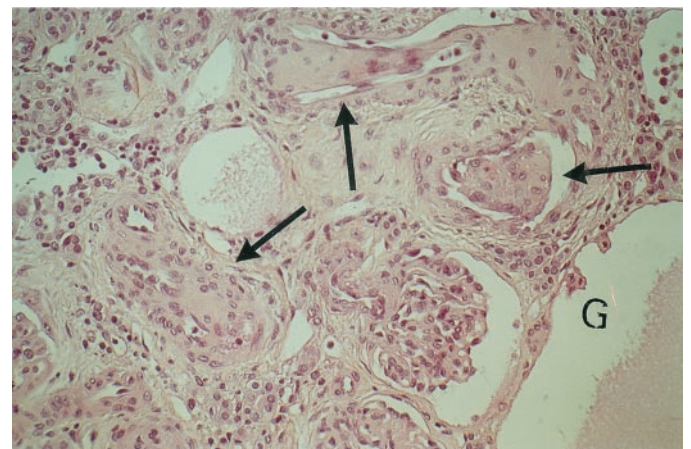
For 25 patients (22%), lupus was not recognized before the biopsy. Among the others, 87 were receiving or had received steroid therapy (median duration, 29 mo; range, 1 to 192 mo), 26 cyclophosphamide, 8 azathioprine, and 44 hydroxychloroquine.

Before or at the time of the renal biopsy, 33 (30%) of 110 patients for whom LA had been sought were positive, 65 (72%) of 90 had significant levels of aCL ( $\geq 15$  GPL units), 24 (22%)

among 107 patients had an APS. APS was statistically associated with LA ( $P = 0.00003$ ; OR = 8.12; 95% CI = 2.96 to 22.3) but not with aCL ( $P = 0.16$ ). Eight patients (7%) had a history of arterial thrombi attributed to APS (cerebral for seven patients, leg in one patient), but there were no main renal artery thromboses. Ten patients (10%) had a history of venous thromboses (of the leg in nine patients, of the arm in one patient) attributed to APS, and 13 women (14% of women) had already had obstetrical manifestations of APS. APS in the absence of APS, *i.e.*, without associated clinical manifestations, was present in 52 patients.

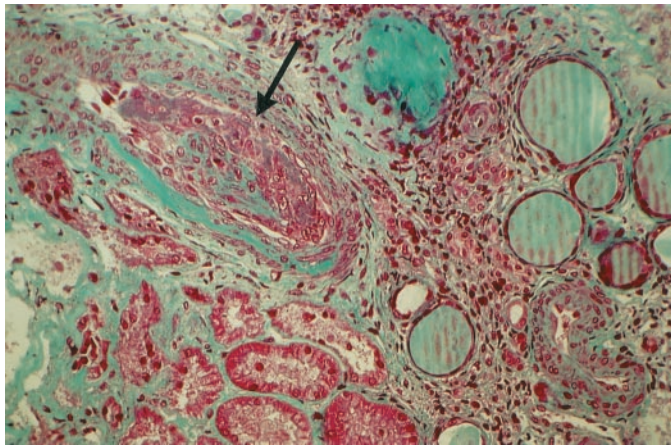
### APSN is Found in SLE and Is Independent of the Class of Lupus Glomerulopathy

Systematic review of the renal biopsies in the 114 patients permitted the identification, side by side with the lesions attributable to SLE, the lesions described in PAPS-related nephropathy. Thus, 36 patients (32%) presented one or more histologic lesions of APSN: 20 patients (18%) had acute lesions of APSN, of whom 9 patients had acute APSN alone, 4 patients with acute APSN and FCA; 27 patients (24%) had chronic lesions of APSN, of whom 17 (15%) had associated FCA; 11 patients had both acute and chronic APSN (Figures 1 through 8). In none of the patients in whom it was identified was FCA the sole lesion suggestive of APSN. A single patient presented a picture of glomerular TMA associated with arteriolar lesions of TMA in the absence of lupus glomerulopathy. It is important to note that no significant association existed between the APSN and the WHO class of lupus glomerulopathy: 8 of the 18 patients having WHO class II lupus nephritis had APSN; 1 of 17 patients with class III; 19 of 60 patients with class IV; and 6 of the 17 patients with class V ( $\chi^2 = 6.75$ ;

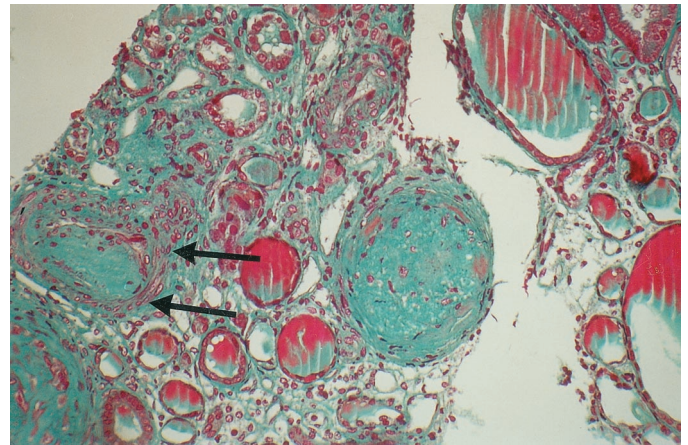


**Figure 1.** Fibrous intimal hyperplasia (FIH) in a renal biopsy from patient with World Health Organization (WHO) class II lupus nephritis. FIH in a focal cortical atrophy (FCA) area. Intrarenal arteries (arrows) showing proliferative and obstructive modifications with fibrous intimal projections or cushions bulging into the lumen, organizing thrombi and endothelialized channels. The glomerulus (G) is pseudocystic and ischemic, with only two small remnants of tuft attached to Bowman's capsule (just above G). Hematoxylin-eosin stain. Magnification,  $\times 200$ .





**Figure 2.** Occlusive lesions of interlobular arteries in FCA in a renal biopsy from a patient with WHO class IV lupus nephritis. Occlusive lesions of interlobular arteries with organizing fibrin thrombi (arrow). Masson's trichrome. Magnification,  $\times 200$ .



**Figure 4.** Occlusive lesions of interlobular arteries in FCA in a renal biopsy from patient with WHO class IV lupus nephritis. Proliferative and occlusive lesions of interlobular arteries with completely fibrotic lesions (arrows). Masson's trichrome. Magnification,  $\times 200$ .

$df = 3$ ;  $P = 0.08$ ). There was no significant difference in the duration of lupus before the renal biopsy between those patients having APSN (median, 35 mo; range, 0 to 192 mo) and those without APSN (median, 30 mo; range, 0 to 132 mo) ( $P = 0.19$ ).

#### *APS and LA Are Associated with APSN in SLE*

The frequency of APSN was 63% in patients with APS (APS group) *versus* only 22% in patients without APS (non-APS group) ( $P = 0.0001$ ) (Table 1). Conversely, APS existed in 45% of patients (15 of 33) with APSN, as compared with only 12% (9 of 74) of those without APSN ( $P = 0.0001$ ).

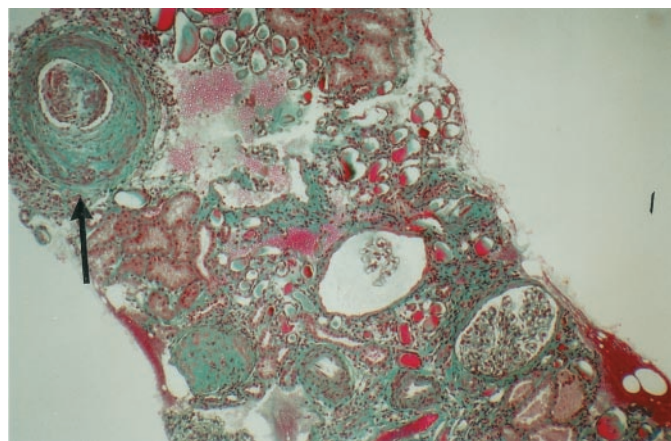
The frequency of APSN was 61% in patients with LA (LA group) *versus* 21% in the group without LA (Table 1). Conversely, LA was present in 56% of patients (20 of 36) with

APSN, as compared with only 18% (13 of 74) of those without APSN ( $P = 0.0001$ ).

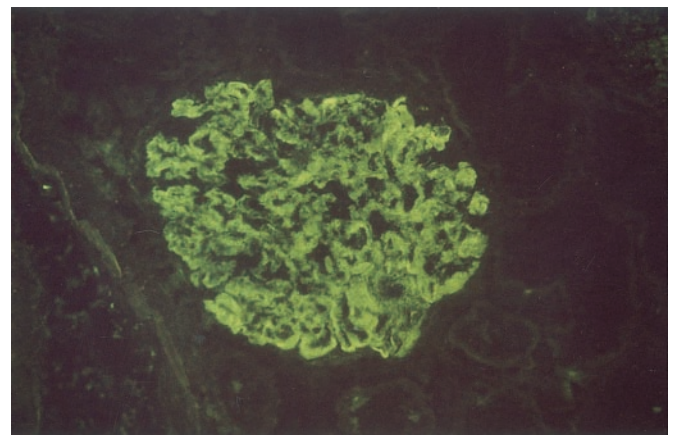
Statistical tests revealed significant associations between the presence of an APS or an LA and the existence of an APSN (OR = 6 and 5.9, respectively;  $P = 0.0001$  for both), a chronic APSN (OR = 3.8,  $P = 0.005$  and OR = 5.7,  $P = 0.0001$ , respectively), an acute APSN (OR = 3.7,  $P = 0.026$  and OR = 3.8,  $P = 0.007$ , respectively), or FCA lesions (OR = 9.2,  $P = 0.0002$  and OR = 8.2,  $P = 0.0001$ , respectively) (Table 1).

However, in contrast with LA, aCL showed no significant association with APSN, chronic APSN, acute APSN, or FCA lesions (Table 1), no matter the level of the aCL titer (median, 28 GPL units [0 to 760] for patients with APSN compared with 23 GPL units [0 to 178] for patients without APSN [ $P = 0.77$ ]).

Finally, only three patients (15%) with neither aCL nor LA

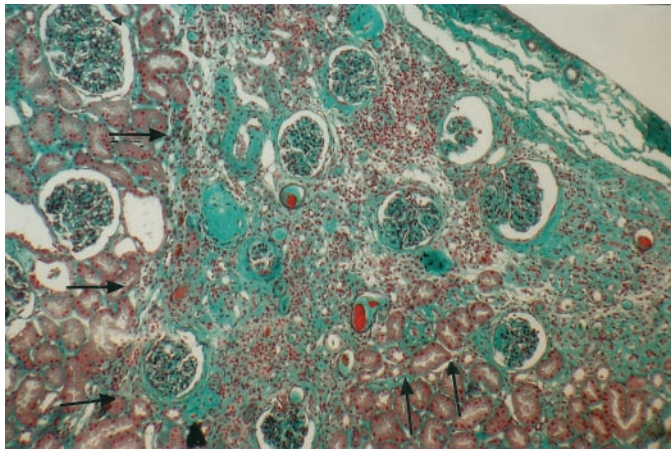


**Figure 3.** Occlusive lesions of interlobular arteries in FCA in a renal biopsy from patient with WHO class IV lupus nephritis. FIH showing endothelial proliferative and luminal occlusive lesions of interlobular arteries with completely fibrotic lesions. Masson's trichrome. Magnification,  $\times 200$ .



**Figure 5.** Surgical renal biopsy from patient with WHO class IV lupus nephritis from the same renal biopsy as in Figure 6. Immunofluorescence of glomerulus from adjacent cortex with widespread distribution of granular IgG. Magnification,  $\times 200$ .



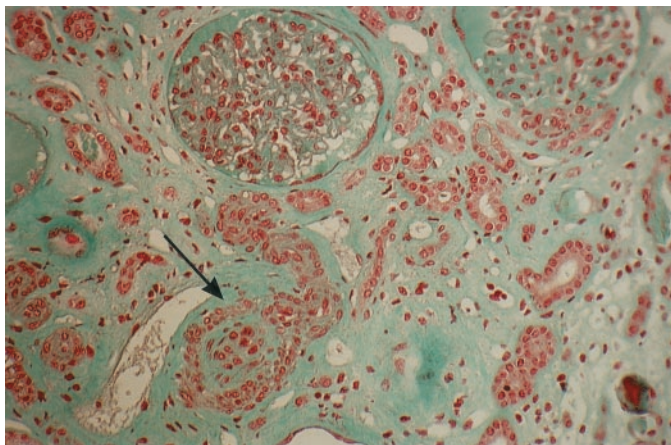


**Figure 6.** FCA in a surgical renal biopsy from patient with WHO class IV lupus nephritis. Focal cortical atrophy involves a triangle (arrows) of the superficial cortex that is accompanied by a depression of the contour of the renal capsule. Glomeruli in region of FCA are retracted without proliferation or any deposits evident by light microscopy. Masson's trichrome. Magnification,  $\times 100$ .

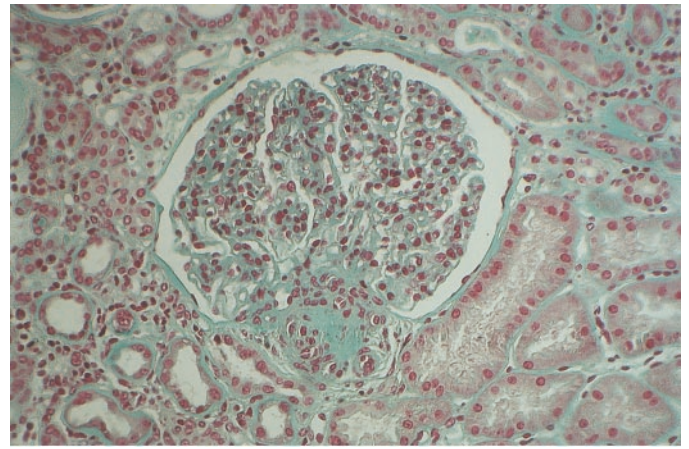
(non-APL group) showed APSN (Table 1), giving a negative predictive value of 85% of aCL and LA in predicting APSN.

#### *Extrarenal Arterial Thromboses and Obstetrical Involvement of APS Are Associated with APSN*

Arterial thromboses attributed to APS were statistically associated with APSN (OR = 8.0), chronic APSN (OR = 8.6), acute APSN (OR = 7.2), and FCA (OR = 12.0) ( $P < 0.05$  for all) (Table 2). Thus, 75% (6 of 8) of the patients having a history of arterial thrombosis had an APSN *versus* 27% (27 of 99) of the patients without APS-related arterial thrombosis ( $P = 0.01$ ); and 18% of the patients with an APSN had a history



**Figure 7.** Thrombotic microangiopathy (TMA) from a patient with WHO class II lupus nephritis, whose renal biopsy was done 4 wk after the acute thrombotic clinical event. The patient showed fibrotic vascular occlusions. Artery in process of fibrous occlusion: lesion is occlusive but still cellular (arrow). Masson's trichrome. Magnification,  $\times 200$ .



**Figure 8.** TMA from a patient with WHO class IV lupus nephritis, whose renal biopsy was done 4 wk after the acute thrombotic clinical event. The patient showed fibrotic vascular occlusions. The glomerular hilar region showing preglomerular arteriolar fibrous occlusion with moderate hyperplasia of the juxtaglomerular apparatus. Masson's trichrome. Magnification,  $\times 200$ .

of arterial thrombosis related to APS *versus* 3% of those without APSN ( $P = 0.01$ ).

Obstetrical complications of APS in the lupus patients in this series were statistically associated with APSN (OR = 6.3), acute APSN (OR = 6.1), and FCA (OR = 9.2) ( $P < 0.05$  for all; Table 2). Conversely, 69% of the female patients having a history of obstetrical accidents attributed to APS had an APSN *versus* only 26% in those without such complications ( $P = 0.004$ ); 30% of female patients with APSN had a history of obstetrical complications of APS *versus* only 6% for those without APSN ( $P = 0.004$ ).

By contrast, no relationship could be demonstrated between APSN or any of its subgroups and the venous thromboses of APS (Table 2).

#### *Patients with APSN Are Significantly More Frequently Hypertensive*

The patients with lupus glomerulonephritis and APSN (or its subgroups) were significantly more frequently hypertensive (60% of patients) than the patients with only lupus nephritis (28% of patients) (Table 3). Conversely, 50% (21 of 42) of hypertensive patients had an APSN compared with only 20% (14 of 69) of normotensive patients ( $P = 0.001$ ). This association between hypertension and APSN is true not only of the milder forms of lupus nephritis (WHO classes II and V) but also for those having class III or IV lupus nephritis ( $P = 0.0034$ ).

Hypertension was examined by logistic regression with APSN, creatinine level at the time of the biopsy, interstitial fibrosis, and WHO class of lupus nephritis included as independent variables. Only APSN (OR = 3;  $P = 0.023$ ) and interstitial fibrosis (OR = 3;  $P = 0.001$ ) were independently and significantly associated with the hypertension (Table 4).

Table 1. APSN and APS features<sup>a</sup>

Group	n (%)	Exclusion	n (%)	OR (95% CI)	P
<b>APSN</b>					
APS	15 of 24 (63%)	non-APS	18 of 83 (22%)	6 (2.4 to 15.2)	0.0001
LA	20 of 33 (61%)	non-LA	16 of 77 (21%)	5.9 (2.5 to 13.8)	0.0001
ACL	21 of 65 (32%)	non-aCL	8 of 25 (32%)	NS	0.98
APL	28 of 76 (37%)	non-APL	3 of 20 (15%)	NS	0.063
<b>Chronic APSN</b>					
APS	11 of 24 (46%)	non-APS	15 of 83 (18%)	3.8 (1.5 to 9.9)	0.005
LA	16 of 33 (48%)	non-LA	11 of 77 (14%)	5.7 (2.3 to 13.8)	0.0001
ACL	16 of 65 (25%)	non-aCL	6 of 25 (24%)	NS	0.95
APL	22 of 76 (29%)	non-APL	2 of 20 (10%)	NS	0.082
<b>Acute APSN</b>					
APS	8 of 24 (33%)	non-APS	10 of 83 (11%)	3.7 (1.2 to 10.3)	0.026
LA	11 of 33 (33%)	non-LA	9 of 77 (12%)	3.8 (1.4 to 10)	0.007
ACL	11 of 65 (17%)	non-aCL	5 of 25 (20%)	NS	0.763
APL	15 of 76 (20%)	non-APL	2 of 20 (15%)	NS	0.5
<b>FCA</b>					
APS	10 of 24 (42%)	non-APS	6 of 86 (7%)	9.2 (3.2 to 26.1)	0.0002
LA	12 of 33 (36%)	non-LA	5 of 77 (6%)	8.2 (2.9 to 23.4)	0.0001
ACL	11 of 65 (17%)	non-aCL	4 of 25 (16%)	NS	0.99
APL	16 of 76 (21%)	non-APL	0 of 20 (0%)	NS	0.02

<sup>a</sup> OR, odds ratio; CI, confidence interval; APSN, antiphospholipid syndrome nephropathy; APS, antiphospholipid syndrome; LA, lupus anticoagulant; ACL, anticardiolipin antibodies; APL, total cases having either LA and/or aCL.

Table 2. APSN and APS-related extrarenal manifestations<sup>a</sup>

Group	n (%)	Exclusion	n (%)	OR (95% CI)	P
<b>APSN</b>					
APS + AT	6 of 8 (75%)	non-(APS + AT)	27 of 99 (27%)	8 (1.9 to 34.3)	0.01
APS + VT	5 of 10 (50%)	non-(APS + VT)	28 of 97 (29%)	NS	0.28
APS + Obst	9 of 13 (69%)	non-(APS + Obst)	21 of 80 (26%)	6.3 (1.9 to 20.6)	0.004
<b>Chronic APSN</b>					
APS + AT	5 of 7 (71%)	non-(APS + AT)	21 of 93 (23%)	8.6 (1.9 to 38)	0.012
APS + VT	4 of 9 (44%)	non-(APS + VT)	22 of 91 (24%)	NS	0.23
APS + Obst	5 of 9 (56%)	non-(APS + Obst)	18 of 77 (23%)	4.1 (1.1 to 15.8)	0.053
<b>Acute APSN</b>					
APS + AT	3 of 5 (60%)	non-(APS + AT)	15 of 87 (17%)	7.2 (1.4 to 37.9)	0.0496
APS + VT	3 of 8 (38%)	non-(APS + VT)	15 of 84 (18%)	NS	0.19
APS + Obst	5 of 9 (56%)	non-(APS + Obst)	12 of 71 (17%)	6.1 (1.6 to 23.5)	0.018
<b>FCA</b>					
APS + AT	4 of 6 (67%)	non-(APS + AT)	12 of 84 (14%)	12 (2.6 to 54.4)	0.0084
APS + VT	3 of 8 (38%)	non-(APS + VT)	13 of 82 (16%)	NS	0.15
APS + Obst	5 of 9 (56%)	non-(APS + Obst)	8 of 67 (12%)	9.2 (2.4 to 35.3)	0.0059

<sup>a</sup> AT, arterial thrombosis; VT, history of large vein thrombosis; Obst, at least 3 spontaneous abortions or one fetal death after 12 wk.

### Patients with APSN Have a Higher Creatinine Level

At the time of the renal biopsy, the SCr of those patients with APSN was significantly higher than that of patients without APSN (median, 100 versus 77  $\mu\text{mol/L}$ ;  $P = 0.0007$ ; Table 3). Only interstitial fibrosis (OR = 2.5;  $P = 0.001$ ) and APSN (OR = 2.6;  $P = 0.0216$ ) were independently and significantly

associated with the creatinine level in a logistic regression model (Table 4).

No other difference could be distinguished among patients in terms of hematuria, proteinuria, or nephrotic syndrome (Table 3). Neither was there any statistical correlation between gender or racial group and the presence of APSN in SLE. The only

Table 3. APSN and clinical features

Parameter	No n (%)	Yes n (%)	OR (95% CI)	P
Hypertension				
APSN	21 of 76 (28%)	21 of 35 (60%)	3.9 (1.7 to 9)	0.001
chronic APSN		14 of 26 (54%)	3.1 (1.2 to 7.6)	0.015
acute APSN		14 of 19 (74%)	7.3 (2.6 to 21.1)	0.0002
focal cortical atrophy		9 of 16 (56%)	3.4 (1.2 to 9.9)	0.026
Hematuria				
APSN	55 of 77 (71%)	26 of 35 (74%)	NS	0.754
Nephrotic syndrome				
APSN	27 of 78 (35%)	12 of 36 (33%)	NS	0.9
Proteinuria (g/d)				
APSN	2.15 (0 to 12)	2.5 (0 to 15)		0.72
Age (yr)				
APSN	28 (13 to 62)	35 (17 to 63)		0.0036
chronic APSN		40 (19 to 63)		0.0017
acute APSN		29 (13 to 63)		0.39
focal cortical atrophy		41 (19 to 62)		0.001
Initial creatinine ( $\mu\text{mol/L}$ )				
APSN	77 (51 to 800)	100 (61 to 700)		0.0007
chronic APSN		95 (61 to 440)		0.056
acute APSN		105 (52 to 700)		0.016
focal cortical atrophy		95 (61 to 440)		0.25

difference was that patients with APSN were older than those without (median age, 35 *versus* 28 yr;  $P = 0.0036$ ). This was also true of the subgroups with chronic APSN or FCA, but there was no difference in age between the lupus patients with

Table 4. Multivariate analysis of hypertension, SCr, and interstitial fibrosis

Parameter	OR (95% CI)	P
Hypertension		
APSN	3 (1.2 to 7.5)	0.023
interstitial fibrosis	3 (1.5 to 6)	0.001
WHO class	NS	NS
SCr	NS	NS
SCr		
APSN	2.6 (1.2 to 6)	0.02
interstitial fibrosis	2.5 (1.4 to 4.3)	0.001
WHO class	NS	NS
hypertension	NS	NS
Interstitial fibrosis		
APSN	5.4 (1.8 to 16.2)	0.003
hypertension	3 (1.1 to 8.1)	0.03
WHO class	1.5 (1.1 to 2.3)	0.048
APS	NS	NS
LA	NS	NS
ACL	NS	NS
lupus duration	NS	NS

<sup>a</sup> WHO, World Health Organization; SCr, serum creatinine.

and without acute APSN (Table 3). Finally, there was no difference in the antecedent corticosteroid or immunosuppressive treatment between those with APSN or its subtypes and those without (median length of steroid, 25 mo [0 to 132 mo] for patients without APSN; 30 mo [0 to 192 mo] for patients with APSN [ $P = 0.36$ ]; 16 [21%] of 77 of patients without APSN *versus* 10 [29%] of 35 of patients with APSN had received cyclophosphamide [ $P = 0.37$ ]; 6 [8%] of 76 of patients without APSN opposed to 2 [6%] of 35 of patients with APSN had received azathioprine [ $P = 0.99$ ]; 31 [41%] of 75 without APSN compared with 13 [38%] of 34 with APSN had received hydroxychloroquine [ $P = 0.76$ ]).

#### Renal Functional Prognosis May Be Worse in Cases of APSN Superadded to Lupus Nephritis

APSN and its subgroups were associated with more extensive interstitial fibrosis (Figure 9), which suggests that the presence of an APSN may worsen the renal functional prognosis in SLE. In the same fashion, there was a statistical association between the extent of interstitial fibrosis and the presence of an APS ( $P = 0.0067$ ), of LA ( $P = 0.0155$ ), or hypertension ( $P = 0.0007$ ) (data not shown). Only APSN (OR = 5.4;  $P = 0.0026$ ), hypertension (OR = 3;  $P = 0.0325$ ), and WHO class (OR = 1.5;  $P = 0.0485$ ) were significantly and independently associated with interstitial fibrosis in a logistic regression model. APS, LA, aCL, and duration of SLE before the biopsy did not reach the 0.05 significance level (Table 4).

Nonetheless, in this retrospective series (median follow-up, 22 mo; range, 0 to 161 mo), we have not been able to dem-



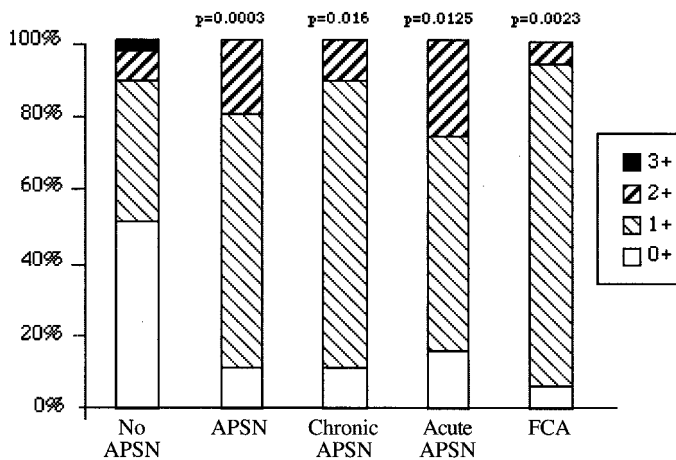


Figure 9. Semiquantitative evaluation of renal interstitial fibrosis in APSN and its subtypes compared with their control groups. Fibrosis is graded from 0 (absence of fibrosis) to 3+ (>50% of parenchyma involved). The groups and their control, e.g., patients with and without APSN or its subgroups, are divided according to the percentage of patients showing each grade of fibrosis. Results of  $\chi^2$  tests comparing the differences between APSN or its subgroups and the control group (no APSN) are shown above.

onstrate that loss of renal function was more rapid in the cases of APSN plus lupus nephritis than in lupus nephritis alone. The number of patients reaching doubling of SCr (2 [6.9%] of 29 patients in the APSN group versus 6 [10.5%] of 57 patients in the group with lupus nephritis alone) were not significantly different. Similarly, the figures for those reaching end-stage renal disease and dialysis in the two groups (6 [10.5%] of 57 patients in the APSN group versus 3 [10.3%] of 29 in the group with lupus nephritis alone) were also not statistically significant. The values of the slope of the curve  $1/SCr$  versus time were calculated according to the formula:

$$\frac{(1/SCr \text{ at end of follow-up} - (1/SCr \text{ at biopsy}))}{\text{Follow-up (in mo)}}$$

In effect, there were no significant differences according to whether APSN was present or not:  $-3.02 \times 10^{-5}$  if APSN versus  $-2.8 \times 10^{-5}$  if no APSN ( $P = 0.78$ ). Furthermore, too few patients received anticoagulants or antiplatelet agents (8 and 15, respectively) for an evaluation of the role of these treatments on renal function to be performed (in addition to the fact that this was a retrospective, nonrandomized study).

### Discussion

The vascular lesions in SLE have been the subject of a revival of interest and of new classifications of lesions in which lesions specific for SLE are included with those whose attribution to SLE-APS is more probable (9–14), particularly arteriolar or glomerular TMA and chronic vascular lesions similar to those we have described in the APSN of PAPS (5). This study contributes to the distinction of those renal vascular lesions attributable to APS from those directly attributable to lupus.

The series of lupus patients studied here is representative of the patients with previously reported lupus glomerulopathy. Thus, the distribution of glomerular lesions (WHO class), the frequency of patients with aCL (72%) and LA (30%), and the percentage of patients with APS (22%) are all in the range of those published in previous studies (15–19). Although the percentage of patients with aCL is within the limits of earlier studies, 72% seems somewhat high. This high prevalence may be related in some part to the fact that before 1995 systematic studies for aCL were only performed on roughly two thirds of the patients on our services. Hence, a possible bias in that the patients whose disease required renal biopsy may have been more extensively studied than the patients before 1995. However, in this study, the tests for aCL and LA were performed in all instances before or at the time of the biopsy and not afterward on the basis of biopsy findings, such as TMA. Thus, a possible bias toward intensified testing of these patients does not modify the qualitative constitution of the groups used and does not influence the statistical associations we have shown here. Finally, it should be remembered that the previous studies represent in part the overall population of lupus patients, rather than the subset with renal disease, as in our series.

The results of this study reveal that APSN is not restricted to primary APS but also exists in the course of secondary APS, notably in SLE (32% of the patients in this study). Up to now, TMA has been the most frequently encountered lesion in patients with SLE-APS (9,20–26). The lesions of chronic APSN have only been described in isolated cases (9,27–29). This series differs in that acute APSN (TMA) was found in 18% of patients, whereas chronic APSN was found in 24%. These differences between earlier studies and this one are probably due to a clearer identification of the lesions of APSN here, because our earlier studies had delineated them in PAPS (5), whereas other authors have not included these lesions, not recognizing their relationship to APS.

The attribution of APSN to APS is supported by the statistical association between APSN and extrarenal APS (Tables 1 and 2). The fact that 22% of patients without extrarenal manifestations of APS had an APSN suggests for us the existence of isolated renal forms (without extrarenal manifestations) of vascular lesions linked to APL in the course of SLE, with the possible exception of livedo, not included in our analysis. Comparison between those patients with APSN + APS (15 patients) and those with APSN without APS (18 patients) revealed no difference in the distribution of any of the lesions between the two groups, suggesting that the differences between the two groups are primarily extrarenal (data not shown). Our results that show the association between LA and APSN and the absence of association between APSN and aCL further strengthen this contention. In effect, we have demonstrated for APSN that LA has a higher predictive ability for vascular lesions than aCL, as has been demonstrated in studies of extrarenal thrombotic manifestations (15–17,30,31). Nonetheless, the evaluation for aCL coupled with that for LA remains of interest in this context, because the negative predictive value of the two tests taken together is estimated to be 85% against the diagnosis of APSN. Three patients had an



APSN (1 chronic APSN without FCA, 1 with acute APSN, and 1 with both acute and chronic APSN) without having APL (Table 1). This suggests that either their APSN was linked to aPL not detected by routine tests for ACL or LA (such as anti- $\beta_2$ -glycoprotein I antibodies, IgM, or even IgA aCL, not systematically determined in this series) or that their APL studies were performed during periods of transient negativity, or alternately that their vascular lesions were related to another, as yet undetermined, intrarenal thrombotic process.

FCA does not seem to be specific for APSN (any more so than TMA or the other lesions of APSN), because FCA may be seen in the course of other renal vascular lesions. However, the principal other causes for these lesions, such as malignant hypertension, have been excluded in this study. Nonetheless, when found in a young patient with lupus and associated with other chronic lesions of APSN (which was always the case in our series), FCA is highly suggestive of the diagnosis of APSN, particularly because this lesion is strongly associated with the presence of an APS ( $P = 0.00019$ ; OR = 9.2; Table 1) or LA ( $P = 0.0001$ ; OR = 8.2; Table 1), especially arterial events and obstetrical complications (Table 2).

Moreover, these results and the association between APSN and obstetrical complications of APS on the one hand, and the extrarenal arterial thromboses on the other (Table 2) support the idea that APSN is a symptom of APS in the same manner as extrarenal thromboses or obstetrical complications.

In the course of this study concerning the APSN of PAPS, no vascular inflammatory lesions of the polyarteritis type were found (5). In this series of lupus patients, a single renal biopsy showed an angiitis with fibrinoid necrosis and associated granulomatous inflammation, with deposits of IgG on immunofluorescence. Thus, this type of lesion turns out to be rare, more likely related to the SLE, as previously reported (3), than to the APS.

Both the association between APSN and extrarenal arterial thrombi and the absence of a link between APSN and extrarenal venous thromboses (Table 2) suggest that there are two subsets of APS patients for whom the location of thrombi primarily affects either venous or arterial/arteriolar sites. This dichotomy might reflect distinct pathophysiologic mechanisms. Ongoing studies are in progress to provide biologic support to this clinical categorization. It should be noted in passing that the lack of association between nephrotic syndrome and APSN was also true in the subset of APS patients with venous thromboses.

As previously described by Kincaid-Smith *et al.* (10,27), we have confirmed the association between APSN and the obstetrical complications of APS in SLE (Table 2). This observation raises the question of a possible causal link between these two types of APS complications.

Moreover, we have shown here that APSN occurs independently of lesions attributable to lupus because its presence is not correlated to the WHO class of the lupus glomerulopathy. Thus we confirm the previously reported results that separate the severity of renal SLE from that of APS manifestations (15–17,32).

The higher median age of patients with APSN than those

with only lupus nephritis relates to the higher age of those with chronic APSN and FCA, rather than to those with acute APSN, who do not differ significantly from those with only lupus nephritis (Table 3). This suggests that the chronic lesions of APSN develop later, probably originating as acute APSN. This interpretation is parallel to the greater age of APS patients in studies of cardiac lesions, either primary or lupus-associated, having cardiac valve lesions, especially thickening, compared with those without valvulopathy or those with vegetations only (33,34).

The association between hypertension and APSN (Tables 3 and 4) leads to the question of whether the hypertension is the cause or the consequence of the APSN. Our earlier study of APSN in primary APS supported arguments in favor of the secondary nature of the hypertension, *i.e.*, the strong stimulation of the renin-angiotensin system and the severity of the lesions of APSN found in patients who were normotensive or only mildly hypertensive (5). Thus it seems probable here that the APSN accounts for the excess of hypertension in patients with lupus nephritis plus APSN over those with lupus nephritis alone.

Univariate and multivariate analyses reveal that APSN is an independent risk factor for the prevalence of hypertension, more severely altered renal function, and more severe interstitial fibrosis (Figure 9 and Tables 3 and 4). Thus, when it is superimposed on lupus nephritis, APSN is an added risk factor for renal morbidity, hypertension, and interstitial fibrosis, all of which are recognized as renal functional prognostic indicators (35–38). Moreover, it is interesting to note that the mere presence of an LA or APS is, in this series of patients with lupus nephropathy, associated with more severe interstitial fibrosis by univariate analysis and, therefore, probably associated with a worse renal prognosis. Nonetheless, we have not been able to demonstrate more rapid loss of renal function in cases with both APSN and lupus nephritis, perhaps because of insufficient follow-up. ESRD related solely to the vascular lesions of APS in the absence of lupus nephritis has indeed been described (28,39). In addition, these results are consistent with those described by Banfi *et al.* (24), who demonstrated that renal vascular involvement in lupus must be considered a pejorative prognostic factor. Thus, APSN may well participate in the progression of renal insufficiency in SLE and must be sought on renal biopsy to direct therapy.

This study has not only established the existence of APS nephropathy within SLE, but it has also shown that these lesions belong to the group of APS-related vascular manifestations independent of SLE. Its presence in conjunction with lupus nephropathy probably augments the risk of evolution toward ESRD, because it is associated with (1) higher creatinine level at time of diagnosis; (2) increased interstitial fibrosis; and (3) systemic hypertension, although it was not possible to demonstrate this formally in this study, probably because of short follow-up. APS nephropathy is thus truly a second renal problem superimposed on the lupus nephropathy. These conclusions demonstrate the necessity of a long-term prospective study to characterize more accurately the contribution of APS nephropathy to reduction of renal mass, a study whose goal

would be to study the effect of treatment directed to the APSN. One might envision that the object of such treatment would be vasoprotective, a goal that is currently infrequently sought in lupus patients, in whom the goal is more often directed toward immunosuppression. Furthermore, this study has demonstrated that APSN is a major component of the APS; therefore, APSN should be included more explicitly within classification criteria for the APS (2). Indeed, from the standpoint of histology, the Sapporo criteria only include thromboses, and therefore only TMA, but ignore the chronic vascular lesions that constitute the majority of APSN lesions.

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