356-363 *Clinical rheumatology*, 1992, **11**, N° 3

Long-Term Follow-up Study of 164 Patients with Definite Systemic Sclerosis : Classification Considerations

M. VAYSSAIRAT, N. BAUDOT, N. ABUAF*, C. JOHANET*

Summary **To evaluate the usefulness of recently proposed schemes of classification for systemic sclerosis an extensive cross-sectional study of a series of 164 consecutive patients with long-term systemic sclerosis was undertaken. There were 47 cases of proximal sclerosis, 93 of distal sclerosis and 24 of complete CREST syndrome. The study included clinical, visceral, immunological and follow-up data. In addition, a quantitative clinical score was calculated for each patient, thus providing indications for prognosis. Data were expressed according to three conventional systems of classification : The ARA system, the diffuse versus limited systemic sclerosis system and the early cutaneous involvement system. The most reliable indications of severe outcome were : proximal sclerosis, trunk skin involvement, presence of anti Scl 70 autoantibody, pulmonary and/or heart involvement and age. Diagnosis and prognosis were not generated by the same items. Prognosis indicators proved more accurate for groups than for individuals. Mortality was 1 death per 149 patient X years of follow-up from diagnosis. We conclude that the ARA criteria for classification should be recognized as a standard, but patients with complete CREST syndrome should be included in the distal group. Other systems of classification, principally 2-way versus 3-way criteria, allow different subsets of patients that correlate with prognosis and the severity of the disease, and could be used for therapeutic purposes.**

Key words **Scleroderma, Systemic Sclerosis, Connective Tissue Disease, Raynaud's Phenomenon, Classification.**

INTRODUCTION

Systemic sclerosis (SS) is a multisystemic disease with numerous clinical and laboratory characteristics resulting in a large variety of expressions and implications (1-7). On the one hand, many patients exhibit mild disease characterized by limited skin induration, Raynaud's phenomenon (RP) and nonlethal visceral involvement. On the other hand, some patients experience a rapidly deteriorating outcome with unrelenting widespread cutaneous fibrotic changes, and kidney, heart or lung impairment leading to severe disability, organ failure or death (8-10). Since 1986, the classification of SS on the basis of either diagnosis or prognosis or both has proved a formidable task and at times confusing, because of the different points of view involved (11-14). The alternative schemes of classification prompted us to report on a large series of 164 patients with definite SS of long-term duration. Our aims were the following : 1) to propose a quantitative individual disease score for each patient in order to identify the indicators that correlated best with the severity of the illness ; 2) to report our accumulated clinical data in the framework of three conventional systems of classification.

PATIENTS AND METHODS

Patients

During the period from June 1984 to July 1988, 1159 patients with Raynaud's phenomenon (RP) were evaluated in our vascular department. Three hundred seventy-four had scleroderma-related disorders, among them 164 with definite SS. Most patients had been under

Department of Angiology, Broussais Hospital, 96 rue Didot, 75014 Paris ; *Department of Immunology. Saint Antoine Hospital, 184 rue du Faubourg Saint Antoine, 75012 Paris, France.

periodical investigation and observation for up to 26 years. Particular attention was paid to the precise age at onset of Raynaud's phenomenon and age at diagnosis of systemic sclerosis. The follow-up period was defined as the time that elapsed between diagnosis and the last examination in our institution.

Diagnosis of systemic sclerosis

SS was diagnosed according to the criteria of the American Rheumatism Association (ARA) (15). We included patients who did not satisfy the ARA criteria but had the complete CREST syndrome requiring the presence of 4 items: C= calcinosis, R = Raynaud's phenomenon, E = esophagal dysmobility, S= sclerodactyly and T = telangiectasia.

Classification

The ARA classification

According to the criteria of the American Rheumatism Association (ARA) (15). (since 1988, the American College of Rheumatology), proximal scleroderma is defined as sclerodermatous involvement proximal to the digits. Distal scleroderma is defined as a combination of two or more of the following: sclerodactyly (sclerodermatous involvement distal to the metacarpo-phalangeal joints), digital pitting scars and bibasilar fibrosis as revealed by chest X-rays.

The diffuse versus limited classification

According to the criteria of Le Roy et al. (13), diffuse SS requires: truncal and acral skin involvement, onset of Raynaud's phenomenon within 1 year of onset of skin changes, visceral involvement and absence of anticentromere antibodies. On the other hand, limited SS requires Raynaud's phenomenon for years, limited skin involvement and high incidence of anticentromere antibody.

The early cutaneous involvement classification

According to the criteria of Masi (14) Giordano (11) and Barnett (12), three subsets are defined, depending on the cutaneous involvement within the first year of presentation i.e. *digital* (finger or toe skin involvement), *proximal extremity* (proximal extremities but not trunk skin involvement), and *truncal*. In our series, this classification was used at the initial presentation in our institution.

Evaluation

All patients underwent an extensive standard work-up during hospitalization. A complete history was obtained for each patient. A general and specific scleroderma-related evaluation was performed which included clinical assessment of the following: area and extent of skin involvement, reflux oesophagitis, sicca syndrome, arthralgia, exertional dyspnoea, and myalgia. The evaluation also included multi-organ screening that comprised chest and hand X-rays (necessary for classification), nailfold capillary microscopy interpreted according to Maricq (16), in order to discern the presence or absence of a scleroderma pattern, oesophageal fibroscopy with manometry, electrocardiogram, and systolic and diastolic arm pressure measurements. In addition, 114/164 patients underwent a pulmonary function test with carbon monoxide diffusing capacity testing, and 118/164 had a labial biopsy interpreted according to Chisholm (17) for the diagnosis of the Sjögren's syndrome. Patients with myalgia underwent electromyography, muscle blood enzyme measurement and muscle biopsy for the diagnosis of myositis. The severity of the disease was evaluated retrospectively in all patients, using a quantitative scale of 0 to 18 (Table I) derived from that proposed by Hughes in 1976 (18) and validated by the same team in several publications (19-21). On this basis, two grades of severity were used, i.e. mild (disease score $\leqslant 7$) and severe (disease score >7).

Autoantibody assays

Of the 164 patients 152 were screened for autoantibodies as follows: 1) antinuclear antibody testing and titration, performed on the human epithelial cell line HEp-2 by indirect immunofluorescence, with a special search for anticentromere and antinucleolar antibodies; 2) detection of antibodies to Scl 70 antigen, performed by immunoblotting assay. Details of the immunologic methods used have been published elsewhere (22).

Statistical analysis

Data were expressed as means ± standard deviation with minimal and maximal ranges. Comparisons between two groups were made with Student's unpaired t-test for quantitative values and the Chi-2 test for comparisons of proportions. Comparisons of more than two groups were made using an analysis of variance for quantitative values (ANOVA and Scheffe F Test) and a contingency table for proportions. Correlations were assessed by the Spearman rank coefficient. For tabulation

Table I: *Criteria of systemic involvement in patients with systemic sclerosis*

System involved	Criteria	Disease score*
Skin	Hand** (proximal to finger)	1
	Face	1
	Trunk	1
	Digital pitting scars	1
Gut	Clinical oesophagitis	1
	Dysmotility (fibromanometry)	1
Lung	Exertional dyspnoea	1
	Bibasilar fibrosis (X rays)	1
	CO transfer factor (<70% predicted)	1
Kidney	Proteinuria and/or creatininaemia >130 micro m/l	3
Heart	Pericarditis and/or ECG changes	3
Other	Sjögren	1
	Myositis	1
	Polyarthralgia	1

* points allotted for involvement; **all patients exhibited sclerodactyly

Table II: *Classification of patients with systemic sclerosis according to three conventional systems*

	Classification		
	ARA	Diffuse/ limited	Early skin involvement
	Proximal	Diffuse	Truncal
	47 (33.5%)	14 (8.5%)	18 (11%)
			Proximal extremity
			35 (21%)
	Distal	Limited	Digital
	93 (66.5%)	150 (91.5%)	111 (68%)
Total	140	164	164

and calculations, we used the Stat View 512 + program from Brain Power INC. and a Macintosh SE computer.

RESULTS

Demographic data

The classification and demographic features of the patients are given in Tables II and III.

It is noteworthy that there was no statistical difference between the 3 groups with proximal scleroderma, distal scleroderma and CREST respectively as regards age at onset of Raynaud's phenomenon, age at diagnosis of SS, and sex ratio. The mean duration of follow-up in our institution was significantly longer for patients with proximal scleroderma than for those with CREST ($p<0.05$). Age at onset of RP was 36 ± 17 years for patients in the mild score subgroup, which did not differ from the severe score subgroup (39 ± 15 years). Age at diagnosis of SS was 51 ± 15 years for patients in the mild score subgroup, which again did not differ from the severe score subgroup (51 ± 13 years). Disease follow-up was 5.4 ± 4 years for patients in the mild score subgroup which differed from the severe score subgroup (8.9 ± 6 years), $p<0.0001$.

Evaluation

Twenty-seven items concerning the clinical and paraclinical evaluation are given in Table IV in order of decreasing sensitivity. The most frequent abnormalities were Raynaud's phenomenon (100%), digital skin induration (100%), and SD pattern on nailfold capillary microscopy (99%) and the presence of antinuclear autoantibodies (94%). There were 117 patients in the mild subgroup and 47 in the severe subgroup according to the results of the disease score. In these two subgroups, the largest differences between the frequency of the 27 clinical and paraclinical items concerned bibasilar fibrosis (19% in the mild subgroup versus 81% in the severe subgroup), exertional dyspnoea (36 versus 85%), face skin involvement (47 versus 91%), proximal scleroderma (17 versus 57%) and heart involvement (6 versus 45%).

The disease severity score

Results of the disease score are given in Table V according to the three systems of classification. The 68 patients with the anticentromere antibody exhibited a significantly lower disease score than the 32 patients with the Anti-Scl 70 autoantibody (5 ± 2.7 vs 8.5 ± 3, $p = 0.001$). In the ARA classification, the severity score for patients with proximal scleroderma was higher than for the group with distal scleroderma ($p<0.05$). The severity score did not differ between distal scleroderma and CREST. In the diffuse versus limited classification, the severity score for patients with diffuse SS was dramatically higher than for patients with limited SS ($p<0.0001$). In the early cutaneous involvement classification, patients with truncal involvement exhibited a higher severity score than patients with proximal extremity cutaneous involvement (8.8 ± 2.7 versus 7.8 ± 3) but this difference was not statistically significant. On the contrary, the difference between truncal and digital subgroups was significant ($p<0.01$). In addition, the difference between proximal extremity and digital subgroups was significant ($p<0.01$).

Table III: *Demographic features and classification of 164 patients with systemic sclerosis*

Diagnostic Group	N	Age at onset of Raynaud's phenomenon mean ± sd (range)	Age at diagnosis of scleroderma mean ± sd (range)	Follow-up from diagnosis mean ± sd (range)	% female
Proximal PSS according to ARA*	47	37 ± 16 (14-80)	48 ± 14 (21-80)	7.8 ± 6	85
Distal PSS according to ARA*	93	37 ± 17 (3-70)	51 ± 15 (18-78)	6.2 ± 4.5	84
Complete CREST not according to ARA*	24	37 ± 18 (1-75)	57 ± 13 (34-76)	4.7 ± 3	92
Total group	164	37 ± 17 (1-80)	51 ± 14 (18-80)	6.5 ± 5 (0-26)	86

* ARA = American Rheumatism Association; ** Age and disease durations given in years.

Table IV: *Frequency of clinical and paraclinical findings in 164 patients with systemic sclerosis. Data are given in order of decreasing sensivity.*

	%
Raynaud's phenomenon	100
Sclerodactyly	100
SD pattern (capillaroscopy)	99
Antinuclear antibody	94
Oesophageal dysmotility	88
Giant capillaries	80
Telangiectasia	75
Digital pitting scars	71
Co transfer factor (<70% predicted)	67
Clinical oesophagitis	65
Face skin involvement	60
Calcinosis	59
Sicca syndrome	56
Arthralgia	53
Exertional dyspnoea	51
Acroosteolysis	50
Anticentromere antibody	44
Sjögren (labial biopsy)	36
Bibasilar fibrosis	33
Proximal scleroderma	29
Anti SCL70 antibody	21
Heart involvement	18
Myositis	7
Association with cancer	5.4
Renal insufficiency	4.4
Antinucleolar antibody	4

Table V: *Comparison by the ANOVA and Scheffe F test of disease scores for 164 patients with systemic sclerosis, grouped according to three different systems of classification*

	Disease score Mean	SD	Range	Statistical significance
Proximal scleroderma n = 47	8.4	3	4-17	p<0.05
Distal scleroderma n = 93	5.4	2.7	1-13	p<0.05
C R E S T n = 24	4.2	2	0-9	NS
Diffuse scleroderma n = 14	9.5	2.1	7-14	p< 0.0001
Limited scleroderma n = 150	5.8	3	0-17	
Truncal scleroderma n = 18	8.8	2.7	4-14	NS
Proximal extremity n = 35	7.8	3	4-17	p < 0.01
Digital n = 111	5.1	2.7	0-13	p<0.01

Treatment

Four of the different treatments given to the 164 patients with SS are indicated in Table VI. Colchicine, high dosage of corticosteroids (> 30 mg of prednisolone a day), D-penicillamine and supportive measures only. Patients with a severe disease score exhibited more frequent indications for D-penicillamine than the others and less frequent indications for treatment with supportive measures only.

Mortality

Seven of the 164 patients died during their evaluation (4%). All were females with a mean age of 71 ± 8 years (range: 62-81). Mortality was 1 death per 149 patient X years of follow-up from diagnosis. According to the ARA classification, 4 patients had proximal scleroderma, 2 distal scleroderma and one had the CREST syndrome. According to the diffuse vs limited classification, only one death was in the diffuse group. Using the early cutaneous involvement classification, 2 deaths were in

Table VI: *Treatment of 164 patients with SS as a function of their quantitative disease score (mild versus severe)*

	Mild score		Severe score		Statistical significance
	n	%	n	%	
Colchicine	53	45	27	57	
Corticosteroids	9	8	7	15	
D-penicillamine	8	7	7	15	p = 0.0047
Supportive measures only	47	40	6	13	(contingency table)
Total	117	100	47	100	

the truncal group, 2 in the proximal extremity group and the 3 others in the digital group. Compared to the other 157 patients, those who died were older (71 ± 8 vs 57 ± 14, p= 0.013), had a higher clinical score (9.3 ± 4 vs 5.9 ± 3, p = 0.0057) and were more often in the severe subgroup (5/47 vs 2/117, p = 0.02). Three patients died of heart disease, 1 of pulmonary hypertension, 1 of infectious pneumopathy, 1 of stroke and 1 of cancer.

DISCUSSION

Classification of SS is required both by the physicians who are responsible for treating such patients and need to know the most potent prognosis indicators, and by researchers, to improve the clarity of their papers and avoid the "Tower of Babel" syndrome, i.e., several interpretations of the same words. Many recent papers have dealt with classification and prognosis outcome indicators in SS, including skin status (11-15), the immunologic profile (6-7, 11, 22-30) and visceral involvement (31,32). All these contributions are not interchangeable, since some of them are conflicting and confusing for authors engaged in research on SS.

The most striking finding in our study is the fact that diagnosis and prognosis are not supported by the same factors. Thus, the 7 most sensitive items, i.e., Raynaud's phenomenon, SD pattern in capillaroscopy, antinuclear antibody, oesophageal dysmotility, giant capillaries and telangiectasia, were not discriminant in separating mild from severe subgroups.

From the diagnostic point of view, no classification has proved more effective than the one proposed by the ARA in 1980 (15) as it exhibits 97% sensitivity and 98% specificity. In this classification, the major criterion (proximal scleroderma) is clearly skin involvement beyond the metacarpophalangeal joints (91% of patients in 15), distal scleroderma being reserved for patients with two or more of the following minor criteria: sclerodactyly (skin involvement distal to the metarcarpophalangeal joints), digital pitting scars and bibasilar pulmonary fibrosis. Furthermore, in the ARA classification, patients with the CREST syndrome (35), suspected secondary Raynaud's phenomenon (36), visceral scleroderma without skin involvement (37), Raynaud's disease with sclerodactylia (38), progressive SS sine scleroderma (39,40) and sine scleroderma systemic sclerosis (11) are not acknowledged to have definite scleroderma when they exhibit less than two of the above three minor criteria. The recently developed immunoblotting technique and nailfold capillary microscopy allow the detection of these probable connective tissue diseases (13,41,42). Most of them have a clinical presentation in which incomplete CREST syndrome precedes cutaneous involvement. None of these various clinical conditions satisfy the ARA criteria for SS but they may evolve into SS, mostly in the distal benign sub-group (36). During our study of 164 patients with definite SS, 210 patients with suspected secondary Raynaud's phenomenon were also evaluated, most of them with incomplete CREST syndrome.

From the prognostic point of view, the methodology used in our study, i.e., cross-sectional analysis and a disease severity score, makes it necessary to allow for several possible biases: 1) Is our series really representative; 2) Is there a possibility that some patients with severe disease were selected out of this study because they had already died? and 3) Is the disease severity score valid? Our institution is not purely a Raynaud's disease clinic, and 80% of the patients in the present series were

referred by clinicians. Consequently, in our opinion, any bias in recruitment would have resulted in the selection of more severely disabled patients, because mild disease is more easily treated locally. Moreover, this possibility seems to be confirmed by the fact that out of a total group of 1159 patients with Raynaud's phenomenon, 374 had scleroderma-related disorders, a much larger proportion than would occur by chance. Another proof is the fact that follow-up was significantly longer for patients in the severe group than for those in the mild group. Thus, severely affected patients were more likely to be treated in our institution.

The mortality given in our series did not represent the overall mortality, as only deaths that occurred during the evaluation were considered, but the mean age of patients who died (71 ± 8 years), and the long mean duration of their disease (10 ± 8 years from diagnosis of PSS) reflect a better prognosis in that series than in those previously reported. Thus, in the series of Barnett et al. (5), the mean age at death was 62 years, i.e., 9 years younger than in our series.

Caution should be exercised in applying the disease severity score proposed by Hughes in 1976. It is not independently validated, as some of the criteria for diagnosis are the same as those defining the disease severity score, but it is the only one available, and is used and quoted in the relevant literature (18-21). In the present study, it had the clear advantage of differentiating between the following: 1) the patients who died from the others; 2) proximal scleroderma from distal scleroderma; 3) patients with anticentromere autoantibody from those with anti-Scl autoantibody; 4) among proximal scleroderma cases, those with trunk involvement from the others; 5) patients treated with D-penicillamine from the others.

The diffuse vs limited criteria currently seem the most popular and widely used system of classification (13). It has the clear advantage of comprising only two groups but it requires criteria other than cutaneous involvement. For example, diffuse SS requires the onset of Raynaud's phenomenon within one year of the onset of skin involvement, early and significant visceral involvement, and the absence of anticentromere antibodies. When using these restrictive criteria, diffuse SS in our series represented only 8.5% of the total group with definite SS. Four patients with truncal cutaneous involvement were, as postulated in (13), assigned to the limited subgroup because of the presence of these restrictive criteria and the presence of anticentromere antibodies. Patients with diffuse SS exhibited a higher severity score than all the other subgroups in all three systems of classification. Such considerations might be especially relevant to therapeutic implication, i.e., benefit/risk evaluation of treatments.

The early cutaneous involvement system of classification proposed by Barnett and Masi (12,14) has the advantage of being simple and unambiguous, as it is based on skin clinical examination only. In our study, patients in the digital group were clearly statistically different from those in the two other subsets, but the truncal and proximal extremity groups were not statistically different as regards the severity score. Therefore, when comparing our series with those of Barnett, some slight differences in methodology exist. Principally, in Barnett (5), unlike with the procedure we applied, the onset of the disease was the onset of Raynaud's phenomenon, and patients with incomplete CREST could be included.

In our opinion, all subsets based upon skin, immunologic and visceral status, only give indications for prognosis, because no classification has yet reached the "gold standard" study design (43) required to formulate an accurate prognosis for the individual patient. For example, it is generally accepted that the CREST syndrome is a benign subset of scleroderma (23, 25-26, 44), but it is especially in this subset that cases of life-threatening pulmonary hypertension occur (35, 45-46). Age might also be an additional factor, as our patients who died were, on an average, 14 years older than the others. Despite their insufficiency, prognosis indicators seemed useful guides to treatment, as we have shown in our series that patients with a severe clinical score more often had indications for D-penicillamine treatment than the others (see Table VI).

In conclusion, when dealing with systemic sclerosis: 1) We recommend clearly stating which patients conform to the ARA classification in which the boundary between proximal and distal scleroderma is the metacarpophalangeal joints; 2) The acronym CREST should only be used for patients with the complete syndrome and with S interpreted as sclerodactyly only; it should be recognized as definite systemic sclerosis and included in the distal or limited categories; 3) Progress in immunology and nailfold capillary microscopy has allowed early detection of patients with Raynaud's phenomenon who are at risk of developing SS in the future; these patients, who do not conform to the ARA criteria for SS diagnosis, should be classified as suspected secondary Raynaud's phenomenon; 4) Avoid confusing the onset of Raynaud's phenomenon with the onset from diagnosis of systemic sclerosis, both dates should be given; 5) Prognosis indicators in SS are numerous and include skin status, immunologic profile, visceral involvement and age, thus allowing different types of subsets which, however, are more accurate for comparison of groups rather than of individuals.

REFERENCES

1. Tuffanelli, D.L., Winkelmann, R.K. Systemic scleroderma. A clinical study of 727 cases. Arch Dermatol 1961, 84, 359-371.
2. Tuffanelli, D.L., Winkelmann, R.K. Diffuse systemic scleroderma. A comparison with acrosclerosis. Ann Intern Med 1962, 57, 198-203.
3. Barnett, A.J., Coventry, D.A. Scleroderma : 1. clinical features, course of illness and response to treatment in 61 cases. Med J Aust 1969, 1, 992-1001.
4. Rowell, N.R. The prognosis of systemic sclerosis. Br J Dermatol 1976, 95, 57-60.
5. Barnett, A.J. Scleroderma (progressive systemic sclerosis): progress and course based on a personal series of 118 cases. Med J Aust 1978, 2, 129-134.
6. Livingston, J.Z., Scott, T.E., Wigley, F.M., Anhalt, G.J., Bias, W.B., McLean, R.H., Hochberg, M.C. Systemic sclerosis (scleroderma): clinical, genetic, and serologic subsets. J Rheumatol 1987, 14, 512-518.
7. Cassani, F., Tosti, A., Bianchi, F.B., Fusconi, M., Selleri, L., Baffoni, L., Veronesi, S., Volta, U., Lenzi, M., Pisi, E. Clinical subsets of scleroderma : relevance of fluorescent and precipitating antinuclear antibodies. Clin Exp Rheum 1987, 5, 23-28.
8. Masi, A., D'Angelo, W.A. Epidemiology of fatal systemic sclerosis (diffuse scleroderma) A 15-year survey in Baltimore. Ann Intern Med 1967, 66, 870-875.
9. Medsger, T.A., Masi, A.T. Epidemiology of systemic sclerosis (scleroderma) Ann Intern Med 1971, 74, 714-721.
10. Medsger, T.A., Masi, A.T., Rodnan, G.P., Benedek, T.G., Robinson, H. Survival with systemic sclerosis (scleroderma). A life-table analysis of clinical and demographic factors in 309 patients. Ann Intern Med 1971, 75, 369-376.
11. Giordano, M., Valentini, G., Migliaresi, S., Picillo, V., Vatti, M. Different antibody patterns and different prognoses in patients with scleroderma with various extent of skin sclerosis. J Rheumatol 1986, 13, 911-916.
12. Barnett, A.J., Miller, M.H., Littlejohn, G.O. A survival study of patients with scleroderma diagnosed over 30 years (1953-1983): The value of a simple cutaneous classification in the early stages of the disease. J Rheumatol 1988, 15, 276-283.
13. Le Roy, E.C., Black, C., Fleischmajer, R., Jablonska, S., Krieg, T., Medsger, T.A.In, Rowell, N., Wollheim, F. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988, 15, 202-205.
14. Masi, A.T. Classification of systemic sclerosis (scleroderma): Relationship of cutaneous subgroups in early disease to outcome and serologic reactivity. J Rheumatol 1988, 15, 894-898.
15. Subcommittee for scleroderma criteria of the American Rheumatism Association diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980, 23, 581-590.
16. Maricq, H.R., Le Roy, E.C., D'Angelo, W.A., Medsger, T.A.Jr, Rodnan, G.P., Sharp, G.C., Wolfe, J.F. Diagnostic potential of in vivo capillary microscopy in scleroderma and related disorders. Arthritis Rheum 1980, 23, 183-189.
17. Chisholm, D.M., Mason, D.K. Labial salivary gland biopsy in Sjögren's disease. J Clin Pathol 1968, 21, 656-660.
18. Hughes, P., Holt, S., Rowell, N.R., Dodd, J. Thymus - dependent (T) lymphocyte deficiency in progressive systemic sclerosis. Br J Dermatol 1976, 95, 469-473.
19. Hughes, P., Holt, S., Rowell, N.R., Allonby, I.D., Dodd, J.K. The relationship of defective cell-mediated immunity to visceral disease in systemic sclerosis. Clin Exp Immunol 1977, 28, 233-240.
20. Hughes, P., Gelsthorpe, K., Doughty, R.W., Rowell, N.R., Rosenthal, F.D., Sneddon, I.B. The association of HLA-B8 with visceral disease in systemic sclerosis. Clin Exp Immunol 1978, 31, 351-356.
21. Greaves, M., Malia, R.G., Milfordward, A., Moult, J., Holt, C.M., Lindsey, N., Hughes, P., Goodfield, M., Rowell, N.R. Elevated von Willebrand factor antigen in systemic sclerosis : relationship to visceral disease. Br J Rheumatol 1988, 27, 281-285.
22. Johanet, C., Agostini, M.M., Vayssairat, M., Abuaf, N. Autoanticorps anti-Scl 70 et anti-centromere. Marqueurs biologiques de 2 variétés différentes de sclérodermie systémique. Press Med 1989, 18, 207-211.
23. Fritzler, M.J., Kinsella, T.D., Garbutt, E. The CREST syndrome : A distinct serologic entity with anticentromere antibodies. Am J Med 1980, 69, 521-526.
24. Tan, E.M., Rodnan, G.P., Garcia, I., Moroi, Y., Fritzler, M.J., Peebles, C. Diversity of antinuclear antibodies in progressive systemic sclerosis. Arthritis Rheum 1980, 23, 617-625.
25. Kallenberg, C.G.M., Pastoor, G.W., Wouda, A.A., The T.H. Antinuclear antibodies in patients with Raynaud's phenomenon : Clinical significance of anticentromere antibodies. Ann Rheum Dis 1982, 41, 382-387.
26. Mc Carty, G.A., Rice, J.R., Bembe, M.L., Barada, F.A. Anticentromere antibody. Clinical correlations and association with favourable prognosis in patients with scleroderma variants. Arthritis Rheum 1983, 26, 1-7.
27. Jarzabek-Chorzelska, M., Blaszcyk, M., Jablonska, S., Chorzelski, T., Kumar, V., Beutner, E.H. Scl 70 antibody - a specific marker of systemic sclerosis. Br J Dermatol 1986, 115, 393-401.
28. Reimer, G., Steen, V.D., Penning, C.A., Medsger, T.A., Tan, E.M. Correlates between autoantibodies to nucleolar antigens and clinical features in patients with systemic sclerosis (scleroderma). Arthritis Rheum 1988, 31, 525-532.
29. Weiner, E.S., Earnshaw, W.C., Senecal, J.L., Bordwell, B., Johnson, P., Rothfield, N.F. Clinical associations of anticentromere antibodies and antibodies to topoisomerase I. A study of 355 patients. Arthritis Rheum 1988, 31, 378-385.
30. Steen, V.D., Powell, D.L., Medsger, T.A.Jr. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. Arthritis Rheum 1988, 31, 196-203.
31. Peters-Golden, M., Wise, R.A., Hochberg, M., Stevens, M.B., Wigley, F.M. Carbon monoxide diffusing capacity as predictor of outcome in systemic sclerosis. Am J Med 1984, 77, 1027-1034.
32. Kostis, J.B., Seibold, J.R., Turkevich, D., Masi, A.T., Grau, R.G., Medsger, T.A.Jr., Steen, V.D., Clements, P.J., Szydlo, L., D'Angelo, W.A. Prognostic importance of cardiac arrhythmias in systemic sclerosis. Am J Med 1988, 84, 1007-1015.
33. Steen, V.D., Ziegler, G.L., Rodnan, G.P., Medsger, T.A. Clinical and laboratory associations of anticentromere antibody in patients with progressive systemic sclerosis. Arthritis Rheum 1984, 27, 125-131.
34. Giordano, M. The CREST acronym and some related problems. Arthritis Rheum 1985, 28, 359.
35. Rodnan, G.P., Medsger, T.A.Jr., Buckingham, R.B. Progressive systemic sclerosis - CREST syndrome : Observations on natural history and late complications in 90 patients. Arthritis Rheum 1975, 18, 423 (abstract).
36. Priollet, P., Vayssairat, M., Housset, E. How to classify Raynaud's phenomenon. Long term follow-up study of 73 cases. Am J Med 1987, 83, 494-498.
37. Crown, S. Visceral scleroderma without skin involvement. Br Med J 1961, 2, 1541-1543.

38. Farmer, R.G., Gifford, R.W., Hines, E.A. Raynaud's disease with sclerodactylia. A follow-up study of seventy-one patients. Circulation 1961, 23, 13-15.
39. Rodnan, G.P., Fennell, R.H.Jr. Progressive systemic sclerosis sine scleroderma. JAMA 1962, 180, 665-670.
40. Barr, W.G., Robinson, J.A. Systemic sclerosis and digital gangrene without scleroderma. J Rheumatol 1988, 15, 875-877.
41. Kallenberg, C.G.M., Wouda, A.A., Hoet, M.H., Van Venrooij, W.J. Development of connective tissue disease in patients presenting with Raynaud's phenomenon : a six-year follow-up with emphasis on the predictive value of antinuclear antibodies as detected by immunoblotting. Ann Rheum Dis 1988, 47, 634-641.
42. Fitzgerald, O., Hess, E.V., O'Connor, G.T., Spencer-Green, G. Prospective study of the evolution of Raynaud's phenomenon. Am J Med 1988, 84 : 718-726.
43. Van der Linden, S.M., Tugwell, P. Pitfalls in assessment of prognosis. Weak study designs are liable to bias. J Rheumatol 1988, 15, 725-727.
44. Velayos, E.E., Masi, A.T., Stevens, M.B., Shulman, L.E. The "CREST" syndrome. Comparison with systemic sclerosis (scleroderma). Arch Intern Med 1979, 139, 1240-1244.
45. Salerni, R., Rodnan, G.P., Leon, D.F., Shaver, J.A. Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (Scleroderma). Ann Intern Med 1977, 86, 394-399.
46. Stupi, A.M., Steen, V.D., Owens, G.R., Barnes, L., Rodnan, G.P., Medsger, T.A.Jr. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. Arthritis Rheum 1986, 29, 515-524.

Received : 25 August 1991 ; Revision-accepted : 10 December 1991
Correspondence to : Professor Michel VAYSSAIRAT,
Hopital Broussais, 96 rue Didot, 75014 Paris, France.