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The nosology of systemic sclerosis: how lessons from the past offer new challenges in reframing an idiopathic rheumatological disorder

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Systemic sclerosis is a rare connective tissue disease characterised by a wide range of clinical manifestations. Compared with previous sets of criteria, the 2013 American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) classification of systemic sclerosis encompasses a broader and more relevant spectrum of the condition. Nonetheless, clinical and prognostic heterogeneity persists among patients fulfilling these criteria. The next task in the classification of systemic sclerosis is the development of new subset criteria that can successfully identify subgroups of patients with distinct prognostic or pathophysiological features. In this Viewpoint we describe the history of systemic sclerosis over the past century with the objective of highlighting the effect of previous nosological debates on efforts to understand and manage this disorder. Rather than seeking to present a systematic review of possible subgrouping for systemic sclerosis in relation to prognosis, we aim to clarify how nosological considerations have influenced our understanding of the cause and prognosis of this so-called idiopathic rheumatological disorder and how aetiological, prognostic, and pathophysiological hypotheses have helped to describe clusters within the disease. By reflecting on past nosological debates and endeavours, we identify challenges for the current initiative to develop a new subgrouping of systemic sclerosis.

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Introduction

Nosology—the definition and naming of disease entities—has long been a subject at the boundary between the management of pathological conditions and the history of medical and biological knowledge.[1] Among other issues, two are crucial in defining disease entities: the aetiological and pathophysiological bases of nosological entities (a given nosological entity is usually associated with a given set of causes); and the practical implications for research and clinical practice of subdivision of a condition into subsets or clusters.[2]

The debate about reframing and renaming non-communicable diseases (NCDs) initiated by Allen and Feigl[3] in *The Lancet Global Health* reminds us that a name change or a new definition can galvanise the re-conceptualisation of an entire condition, with far-reaching consequences. For example, in offering a clear consensual definition for idiopathic pulmonary fibrosis and a better description of non-specific interstitial pneumonia, the updated 2013 definition of idiopathic interstitial pneumonia[4] has offered an opportunity to improve the understanding of the mechanisms underlying the pathogenesis of these disorders. It has also enabled antifibrotic therapies to be adapted for the proper clusters of patients, on the basis of CT results and clinical considerations, thus allowing substantial progress in the management of idiopathic pulmonary fibrosis.

In the field of rheumatology, systemic sclerosis can be considered a typical rheumatological NCD, a chronic and severe disorder of complex and unknown cause.[5] The history of its nosology illustrates the great consequences of naming and classification. The multiple subgroupings and names of systemic sclerosis over time have shaped aetiological and prognostic hypotheses successively proposed for this systemic disorder and, alternatively, comorbidities such as cancers associated with systemic sclerosis, have helped to adapt the management of specific subgroups of patients.

A new international clustering initiative for systemic sclerosis is being developed to determine the most useful subgrouping within the entity defined by the 2013 American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) classification.[6–10] Using an historical perspective, this Viewpoint aims to clarify how nosological considerations of systemic sclerosis have influenced our understanding of the aetiology and prognosis of this so-called idiopathic rheumatological disorder and the way aetiological, prognostic, and pathophysiological hypotheses have conversely helped to highlight clusters within the disease, and to discuss the prospect of a new subgrouping enriching our view of systemic sclerosis.

Acrosclerosis, scleroderma, and systemic sclerosis: nosological shifts around a rare autoimmune disorder

In the early 1900s scleroderma (at that time mostly spelled sclerodermia) was mostly understood as a dermatological disorder. Hutchinson[11] highlighted the difference between morphea (localised scleroderma) and diffuse scleroderma or acroscleroderma (previously spelled acrosclerodermia), pointing out the unusual frequent association of acroscleroderma with the vascular changes observed in Raynaud's disease.[12] Morphea or localised scleroderma was therefore separated very early on from other forms of scleroderma (figure 1). Separately, from a strictly dermatological point of view, without any visceral considerations, a distinction was made among

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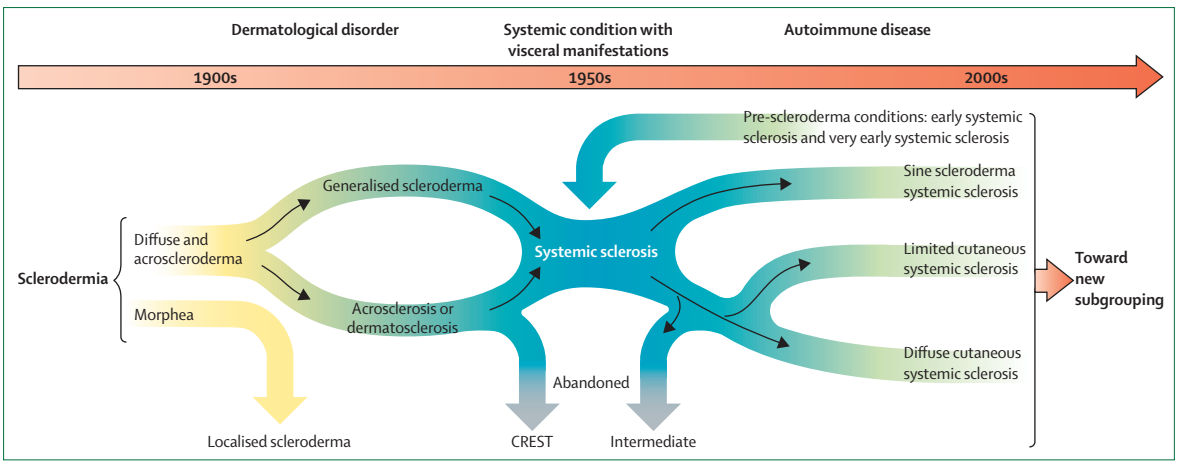


Figure 1: **Naming flow of sclerodermas and systemic sclerosis over the past century**

the sclerodermas: acrosclerosis on the one hand, defining the association of sclerodactyly (or dermatosclerosis) with distal vascular changes, and a rapidly spreading scleroderma with generalised cutaneous involvement and a poorer prognosis on the other.[13,14]

Sellei[13] and then O'Leary and Waisman[14] assumed acrosclerosis to be a unique disease, and not simply the coincidental co-occurrence of Raynaud's syndrome with sclerodactyly. Ingram[15] also stressed the necessity of making a clear distinction between acrosclerosis or distal vascular scleroderma, and diffuse or generalised scleroderma which did not begin on fingers but on wrists and was more aggressive.[16] The clear recognition of these two distinct nosological conditions also coincided with the definitive loss of the "i" from the name. At first, the analysis of the visceral involvement seemed to re-enforce the difference between acrosclerosis and generalised or diffuse scleroderma. O'Leary and Waisman[14] highlighted the different prognosis of these two clusters, pointing out that acrosclerosis affected predominantly women, and was associated with Raynaud's phenomenon, visceral lesions, and a good prognosis.

By contrast, generalised or diffuse scleroderma affected both sexes, was less associated with Raynaud's phenomenon, had a poorer prognosis, and, paradoxically, visceral lesions were initially thought to be rare.[17] Gastrointestinal lesions were specifically noticed in acrosclerosis at the beginning of the twentieth century,[18–20] and only later on in generalised scleroderma.[21] Heart involvement was carefully documented by Goetz[22] in 1951 in generalised scleroderma. Lloyd and Tonkin[23] enriched the literature on pulmonary fibrosis. Given these observations on visceral lesions, a shift in the controversy on scleroderma clustering emerged; if visceral involvement tends to be similar in acrosclerosis and generalised scleroderma, should these conditions be reunited under the same name?

In 1959, Jablonska and colleagues[16] did a systematic analysis of vascular changes, skin involvement, and, most importantly, visceral changes in 45 patients with scleroderma. Their explicit objective was to prove that acrosclerosis was a subgroup of scleroderma with marked vascular changes but not a disease in its own right. They concluded that acrosclerosis was a variety of diffuse scleroderma (ie, in contrast with morphea or localised scleroderma) preceded or accompanied by Raynaud's phenomenon. In almost all cases there were simultaneous features of both so-called acrosclerosis and diffuse scleroderma, which made a clear distinction between the two diseases impossible. They noted that "generalisation of the sclerotic changes in the skin occur in any case of scleroderma, including those which begin in the hands and are preceded or accompanied by Raynaud's phenomenon".[16] Therefore, the terms scleroderma, acrosclerosis, or sclerodactyly became apparent misnomers[24] that no longer adequately described the whole picture of the condition.[17] As the term sclerosis was already in use, the name systemic sclerosis, as first suggested by Goetz,[19] was endorsed, stressing the possible severe visceral manifestations of the disease and including the internal organ involvement in the very name of the disorder.

Consensual views of the disease for research purposes and early diagnosis

A tentative but persistent distinction remained between a slowly spreading systemic sclerosis, which shared features with the previously named acrosclerosis, and a rapidly progressive condition with a poorer prognosis named progressive systemic sclerosis.[22] Nevertheless, since the 1960s most authors considered systemic sclerosis and progressive systemic sclerosis to be the same entity encompassing the outdated acrosclerosis and the generalised scleroderma.[25]

The conceptual shift from perceiving scleroderma as a dermatological disorder to perceiving it as a systemic condition with a wide spectrum of clinical presentations, allowed the emergence of a new entity (figure 2). In 1962, Rodnan and Fennell[26] reported four patients with systemic sclerosis with visceral involvement (digestive, myocardial,

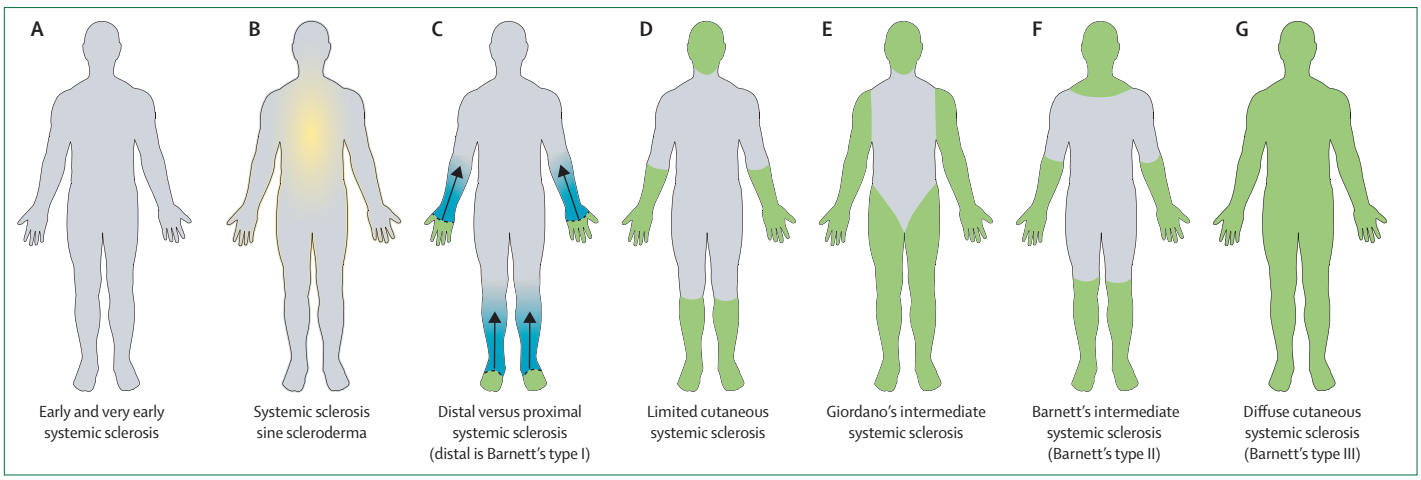


Figure 2: **Skin-derived clustering of systemic sclerosis**
The limited versus diffuse cutaneous systemic sclerosis subsets (D and G) as proposed by LeRoy are currently the most widely used skin-driven sub-classification.

or lung lesions) but with no evidence of skin fibrosis, thereby enriching the systemic sclerosis nomenclature with the concept of systemic sclerosis sine scleroderma. This understanding of the disease as a systemic disorder also coincided with the identification of autoantibodies, with focus on antinucleolar antibodies.[27] In 1968, Rothfield and Rodnan[28] showed that the specific pattern of fluorescence of antinuclear antibodies could help to confirm the clinical diagnosis of systemic sclerosis. In 1980, Moroi and colleagues[29] brought to light anticentromere antibodies and their frequent association with a variant of systemic sclerosis, the Calcinosis-Raynaud phenomenon-Esophageal dysmotility-Sclerodactyly-Telangiectasia (known as CREST), which was first described by Winterbauer[30] in the English literature,[30,31] inherited from a 1910 observation by Thibièrge and Weissenbach.[32]

In 1980, Masi and colleagues from the Subcommittee for Scleroderma Criteria of the American Rheumatism Committee[25,33] proposed standardised clinical classification criteria with the objective of establishing a consensus on inclusion criteria, to enable comparison between groups of patients from different centres, especially for research purposes. A consensual classification of the disease was therefore adopted, including proximal scleroderma (sclerodermatous skin changes proximal to the metacarpophalangeal or metatarsophalangeal joints) as a major (sufficient) criterion, or at least two of the three minor criteria: bibasal pulmonary fibrosis, digital pitting scars, and sclerodactyly. This clinical picture was further refined in 1988 by LeRoy and colleagues,[34] who reintroduced a skin-driven subgrouping of diffuse versus limited cutaneous systemic sclerosis,[34] on the basis of prognostic considerations in longitudinal studies,[35] while maintaining the understanding of the subgroups as parts of a unique but heterogeneous disease. The concept of an intermediate cutaneous systemic sclerosis was proposed by Giordano and colleagues[35] but was finally not adopted. Another skin-driven subgrouping was suggested by Barnett and colleagues,[36] separating three types of systemic sclerosis depending on the extent of fibrosis (figure 2). The dichotomous subgrouping proposed by LeRoy and colleagues[34] in 1988 was finally preferred to other approaches, including CREST, which were abandoned.

As early management of visceral involvement and treatment were believed to improve survival rates, in 2001 LeRoy and Medsger[37] proposed the concept of early systemic sclerosis, on the basis of the association of the hallmark feature of Raynaud's phenomenon with a scleroderma-type nailfold capillary pattern or scleroderma selective antibodies. This concept of early systemic sclerosis introduced the pre-scleroderma stage of limited systemic sclerosis, that differed from limited cutaneous systemic sclerosis by the absence of cutaneous involvement. It also differed from Rodnan and Fennell's[26] 1962 systemic sclerosis sine scleroderma, which involved visceral manifestations of the disease even in the absence of cutaneous changes.[38] In 2011, Avouac and colleagues[39] of the European Scleroderma Trials And Research (EUSTAR) group went further by defining a core set of preliminary criteria necessary for a very early diagnosis of systemic sclerosis on the basis of Raynaud's phenomenon, puffy fingers or antinuclear antibodies. They thus stratified the risk of developing systemic sclerosis on the basis of the results of capillaroscopic findings and more specific immunological investigations. This new approach for the diagnosis of systemic sclerosis allowed a more informed follow-up of patients who were most at risk of developing this systemic disorder. Nonetheless, a systematic early diagnosis could also lead to misinterpretation, as some patients might never develop authentic systemic sclerosis, with subsequent anxiety among patients and an increased cost of screening.

In 2013, the ACR and the EULAR established a committee to provide a joint proposal for new classification criteria for systemic sclerosis.[6] Their objective was to develop criteria that could include both patients in the

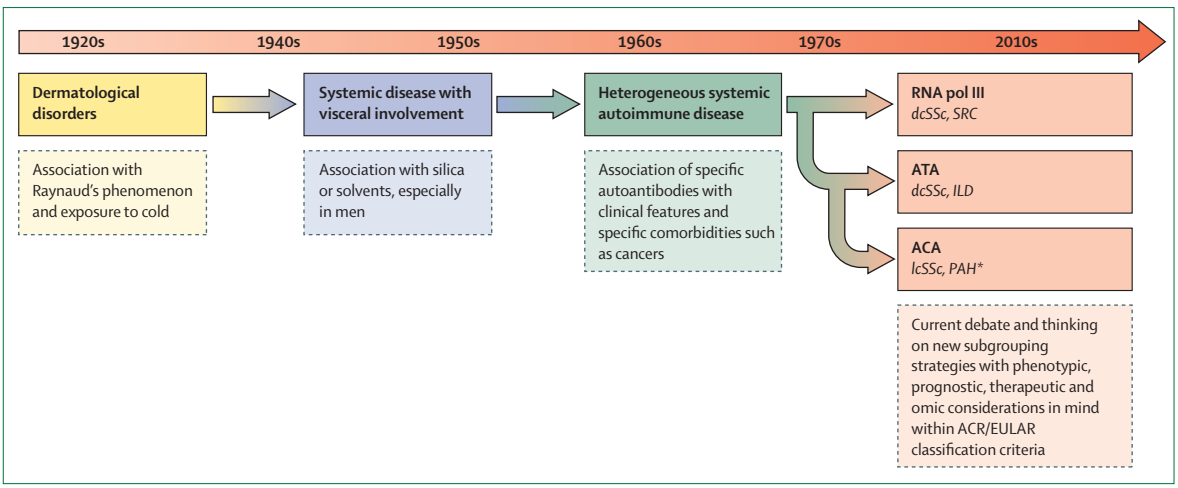


Figure 3: **From the history of the nosology and understanding of systemic sclerosis to the current debate on a new subgrouping strategy**
RNA pol III=anti-RNA polymerase III antibodies. dcSSc=diffuse cutaneous systemic sclerosis. SRC=scleroderma renal crisis. ATA=antitopoisomerase antibodies. ILD=interstitial lung disease. *The association of anticentromere antibodies (ACA) with pulmonary arterial hypertension (PAH) is less concordant in the literature than their association with limited cutaneous systemic sclerosis (lcSSc).

early and late stages of the disease. These new criteria integrated vascular, immunological, and fibrotic manifestations and were established as feasible in daily practice. They were also far more sensitive and specific than the previous 1980 ACR classification criteria.

Each of these definitions, and each new naming of the disease accompanying them, has influenced research on the possible causes of systemic sclerosis in the past hundred years and, conversely, prognostic considerations, more refined clinical phenotyping, better characterisation of autoantibody status, and some aetiological hypotheses have served to highlight specific subgroups, influencing nosology and management (figure 3).

Nosology and its effect on the search for the cause of systemic sclerosis

Exposure to crystalline silica is now identified as an environmental risk factor for systemic sclerosis. Nonetheless, the gradual emergence of this understanding depended on the changing nosological boundaries of the disease. In 1914, Bramwell,[40] a Scottish physician in Edinburgh, UK, published a case series of nine patients with diffuse scleroderma. Bramwell stressed the rarity of the condition and its unusually frequent occurrence in stonemasons. For the first time, diffuse scleroderma was thus addressed as an occupational, environmentally driven condition. As the name of the disease was the misnomer (scleroderma), with the disease being still widely accepted as a dermatological disorder (figure 1), the intriguing high prevalence of scleroderma in stonemasons directed the search for causes towards a skin-mediated process. Although Bramwell observed the onset of the disease in the stonemasons' hands, he emphasised the holding of chisels or hammers during cold weather as a possible cause for the disease. He made no mention of silica exposure, even though we can assume that stonemasons had both cutaneous and respiratory exposure to crystalline silica particles during stone-cutting. Moreover, five of the nine patients presented by Bramwell were stonemasons, and one was a coal miner, another occupation exposed to silica inhalation. Bramwell considered scleroderma as a dermatological condition. He noticed no systemic manifestation nor any visceral involvement, especially no lung involvement, except for pleurisy and pneumonia in one patient.

By contrast, in 1957 Erasmus[41] examined the incidence of scleroderma in South African underground mineworkers, with a specific interest in pulmonary manifestations in a historical and local context, in which respiratory occupational health was of primary concern. From the beginning, Erasmus stressed the importance of properly naming the disease. He deplored the ambiguity of the term scleroderma, and insisted on the terms generalised or diffuse scleroderma to denote that "internal organs as well as skin [were] involved in the disease process". Considering scleroderma as a systemic disease with pulmonary involvement coexisting with features of silicosis in underground gold miners, Erasmus proposed the hypothesis that mining was a predisposing or precipitating factor for systemic sclerosis. He recognised the importance of the work that Bramwell did in 1914 as the first occupational lens on the disease, but he also highlighted the role of silica dust exposure on Bramwell's patients. From the 1957 publication emerged the entity of Erasmus syndrome, characterising the association of systemic sclerosis and crystalline silica exposure with or without silicosis. Since the late 1970s, studies have also hypothesised that other environmental and occupational exposures, such as solvents, might constitute risk factors for developing systemic sclerosis.[42]

A paradigm shift in the late 1960s to viewing systemic sclerosis as an auto-immune disorder, linked to the

production of autoantibodies targeting autoantigens, further shaped our view of its aetiology and management (figure 3). Immunological studies from the past decade have revealed cases of anti-RNA polymerase III antibodies associated with synchronous neoplasia at the time of diagnosis of systemic sclerosis.[43] These results have been confirmed epidemiologically,[44] and the underlying molecular mechanisms have been clarified thanks to fundamental and translational research showing specific targeting of tumour antigens by these autoantibodies. Both highlighting this specific association and revealing a subgroup that some would consider as paraneoplastic systemic sclerosis have changed the standard of care for these patients. These findings have resulted in calls for systematic screening for cancers in patients recently diagnosed with systemic sclerosis who are positive for anti-RNA polymerase III antibodies, although the prevalence of cancers remains low even in this subgroup.

Beyond cancers, the association between anti-RNA polymerase III antibodies and scleroderma renal crisis has influenced the standard of care for this subgroup of patients.[45] Careful automonitoring of arterial pressure has been recommended for these patients to detect any early sign of scleroderma renal crisis, which would require the introduction of angiotensin-converting enzyme inhibitors that can dramatically improve the prognosis of these patients.[46,47] Considering systemic sclerosis as an autoimmune disorder has also paved the way for genetic studies identifying susceptibility loci as risk factors for developing the disease, with a specific interest in genes involved in the regulation of adaptive and innate immunity.[48] In summary, the emergence of new antibodies since the identification of antinuclear antibodies in patients with systemic sclerosis, and their association with clinical features, have allowed for new clustering strategies.[8,49]

Systemic sclerosis subgroups: the challenge of diversifying evaluation tools and clustering strategies

In 2015, Pope[50] suggested that new subset criteria within the ACR/EULAR 2013 classification should be developed, stressing the constraints of the dichotomous limited versus diffuse view of the disease, noting that patients with early limited cutaneous systemic sclerosis could evolve to a diffuse cutaneous systemic sclerosis and that skin fibrosis in diffuse cutaneous systemic sclerosis could regress. In 2015, Ligon and Wigley[51] argued that focusing on skin manifestations alone clearly missed essential features of the disease process, such as serological biomarkers, other organ involvement, and the rapidity of disease progression. They suggested that the limited versus diffuse subsets from LeRoy's 1988 subgrouping strategy, constituted a "black and white" view of systemic sclerosis whereas a "technicolor", ie, a more subtle and heterogeneous characterisation of the disorder, would be more accurate. Using a qualitative content analytic approach, Johnson and colleagues[8] also stressed the necessity of a new subgrouping and synthesised the views of international systemic sclerosis experts on the main challenges and objectives of these upcoming new subsets of systemic sclerosis. Three thematic areas arose from this analysis. First, the new clusters should help to directly improve management of patients with systemic sclerosis who require treatment, early investigation, and monitoring over time. Second, the new subgrouping should be designed as a research and communication tool, allowing for a reduction in heterogeneity of the disease by improving sample selection and offering a more accurate view of the disease to educate patients, trainees, and health-care professionals. Finally, the challenge for this new subgrouping would be to improve the correlation between disease subsets and prognosis, in terms of survival and internal organ involvement.[8,50]

With respect to these considerations, none of the previous subgroupings of systemic sclerosis included gender in the clustering design. Studies based on the largest worldwide multicentre cohort of the EUSTAR group have confirmed that the disease appears to be strikingly more severe in men.[52] Although systemic sclerosis is more common in women, men affected by the condition have a higher risk of severe cardiovascular involvement. Thus, we are encouraged to maintain a greater awareness of gender in the clinical decision-making process.

Exploring this gender gap also entails broadening the field of research on systemic sclerosis. As men and women experience distinct exposures (eg, solvents, silica dust) because of occupational and possibly extra-occupational activities, the gender difference in systemic sclerosis might be explained once we gain a better understanding of the pathophysiological processes involved in toxicant-associated autoimmunity. A gendered approach to aetiology could also benefit from evaluation tools borrowed from the social sciences (eg, quantitative survey research and ethnographic approaches). These tools could provide a better knowledge of potential environmental risk factors and social determinants. As argued in *The Lancet*, proper reporting of sex and gender should be an important task for medical research in general.[53–55] Shim[56] urges us to rethink the epidemiological multifactorial model, which dominates this discipline, to highlight differences between and within subpopulations affected by chronic diseases. Among other differences, sex and gender deserve not to be addressed as black boxes (ie, entities to be taken for granted) but, on the contrary, questioned to understand their internal mechanisms.[57] The general considerations raised by Shim on epidemiological variables, usually handled as patients' individual characteristics, urge us to investigate how differences between women and men are produced in systemic sclerosis and "what *exactly* about…sex/gender contributes to [this] chronic disease".[56] Of course, inclusion of gender in a new clustering of systemic sclerosis should not lead to an oversimplified dichotomous black and white view of the disease.[51] The relationship between sex and gender

and systemic sclerosis is likely to be more complex than it seems, especially considering that diffuse cutaneous systemic sclerosis and antitopoisomerase antibodies tend to be more frequent in men. In a 2019 EUSTAR study exploring phenotype-driven hierarchical clustering, cluster C1 in the study, which had the lowest prevalence of men (6%), showed the best survival, whereas cluster C6 with the highest prevalence of men (21%) had the worst survival, stressing that even in more subtle clustering analyses, sex and gender still influence prognosis, and further deciphering the possible multiple reasons behind these results remains challenging.[9] Integrating sex and gender in a hierarchical approach with autoantibodies and cutaneous subsets might also help to explore this issue.

In a similar vein, cohort studies evaluating the adverse prognosis of scleroderma among African Americans, have shown the importance of socioeconomic status and socioeconomic determinants of health (marital status, education, employment, health insurance status) as independent predictors of systemic sclerosis severity, independent of race. These studies showed that in this idiopathic disorder social determinants are of interest alongside clinical, serological, and genetic predictors.[58,59] Considering the reframing of NCDs suggested by Allen and Feigl[3], Vijayasingham and Allotey[60] proposed a conceptual extension. If gender, social factors, and, in the case of systemic sclerosis, environmental factors and coassociated NCDs, such as synchronous cancer in some anti-RNA polymerase III antibody-related sclerodermas, affect the onset of the disease, these factors might also influence scleroderma's course and severity, and the patient's quality of life.

Autoantibodies, which contributed to conceptualising systemic sclerosis as one disease in the late 1960s,[28] remain a cornerstone in the debate surrounding the upcoming subgrouping of systemic sclerosis.[8,59,51] The progressive identification of antibody patterns associated with an increased risk of specific visceral involvement, has offered new diversity among patients with systemic sclerosis: the association of anti-RNA polymerase III antibodies with scleroderma renal crisis and with diffuse cutaneous systemic sclerosis,[45,49] or that of anticentromere antibodies with limited cutaneous systemic sclerosis and with a possible increased risk of pulmonary arterial hypertension.[61] There is also evidence for increased risk of interstitial lung disease in patients with antitopoisomerase antibodies, anti-U11/U12 RNP antibodies, or anti-Th/To antibodies (figure 3).[51,61–63] Therefore a more refined phenotyping of patients and better characterisation of the relationship between autoantibody profile and prognosis might be needed.[63] As each antibody subtype usually excludes others, from a practical viewpoint, an antibody-based hierarchical clustering associated with other parameters such as skin involvement might appear convenient.[8,49,63] However, a cluster analysis of the EUSTAR database showed that serological heterogeneity existed within apparently homogeneous clinical clusters.[9] As clinical subsets and antibodies have been found to be variable on the basis of genetic background, generalisation of an antibody-based clustering might have some limits. Nonetheless, clinical trials such as the successful randomised placebo-controlled SENSCIS trial,[64] evaluating the efficacy and safety of nintedanib in systemic sclerosis-associated interstitial lung disease and its ability to reduce the decline of forced vital capacity, included a stratification based on antitopoisomerase antibodies in its randomisation strategy. This inclusion shows that antibody status is a practical and relevant way to define homogeneous groups among patients with systemic sclerosis, especially for clinical trials.

Conclusion

In 1903, at an early stage in the nosological history of systemic sclerosis, Nixon[65] argued that "one likes…to minimise the points of contrast between one patient and another, and to bring out into high relief the similarities, so that the final triumph may be achieved of labelling a new disease with a new name, and suggesting a new preparation…as the new remedy". Although tinted with slight irony, this statement illustrates the close association of systemic sclerosis clustering with therapeutics. Until now, none of the previous subgroupings of this disease were shaped with direct therapeutic considerations in mind. Therapeutic trials nowadays still use the old skin-driven, diffuse versus limited cutaneous systemic sclerosis subgrouping in their inclusion criteria (figure 2), although many of them also endeavour to refine this approach by adding limitations on the basis of minimal or maximal fibrosis skin score values, specific disease course-based subgroups (eg, early *vs* late systemic sclerosis), or like the SENSCIS trial, antibody status.[64,66] Using these not fully endorsed subgroup definitions might help to produce new cluster strategies and reinforce the association between subgroups within systemic sclerosis and therapeutic considerations. In the SENSCIS trial, the authors discussed the effect of including patients with limited cutaneous systemic sclerosis, which might have led to a smaller annual rate of decline in forced vital capacity than assumed in the sample size calculation. Although the trial produced a positive result, bringing some optimism to the future management of systemic sclerosis, this statement from the paper's authors shows that even in trials based on single organ impairment (in this case, pulmonary involvement), the question of clustering matters.[64]

The best methods to define the new subgrouping are still a matter of debate. Methodological breakthroughs and innovative subgrouping techniques have emerged and include principal component analysis based on autoantibody status and titres,[7,63] machine learning-based phenotype-driven hierarchical clustering,[9] and systemic sclerosis subsets based on molecular patterns, gene expression profiles, and combined omics technologies from the perspective of personalised medicine.[10,67,68] These approaches could accelerate progress by successfully

Search strategy and selection criteria

We identified references for this Viewpoint through searches of PubMed with the search terms "systemic sclerosis", "scleroderma", "sclerodermia", "nosology", and "classification" from inception of the database until June, 2019. We also identified articles through searches of the authors' own files. The final reference list was generated on the basis of its relevance to a descriptive account of the effect of the various nosological debates and efforts to the understanding and management of systemic sclerosis. Hence, this approach was conceived as a narrative review, rather than as a systematic one.

identifying subgroups of patients with distinct prognosis or pathophysiological processes, beyond the dichotomous skin-driven sub-grouping that still lingers in 2019. However, these approaches need to be synthesised or combined to shape practical and easy-to-use subsets of systemic sclerosis as there is also a risk of building too complex or inapplicable clustering. Whatever the final form, the new subgrouping of systemic sclerosis is needed as a lever to ensure that this poorly understood condition earns the attention it deserves.

Contributors

AL and CCav wrote the first draft of the manuscript. RE, CCaz, AB, NB, GC, MdSR, P-AR, EH, VS, and PJ corrected, highlighted new key points and references, and added substantial modifications to the manuscript.

Declaration of interests

EH received speaking fees from Actelion Pharmaceuticals, GlaxoSmithKline, and Bayer outside of the current study. VS reports receiving personal fees from Grifols and grants from Grifols, Pfizer, Actelion Pharmaceuticals, Octapharma, Shire, and GlaxoSmithKline outside of the submitted work. PJ received personal fees from Bayer and personal fees and non-financial support from Actelion Pharmaceuticals outside of the current study. CCav and P-AR were involved in the Silicosis Project, Centre for European Studies and Comparative Politics, Sciences Po (Paris, France), sponsored by the European Research Council (ERC); (grant number ERC-2011-ADG_20110406, project ID 295817).

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