Chapter 1
Historical Perspective

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Keywords Historical perspective • Key historic figures • Landmarks • Pathogenesis • Scleroderma • Timeline • Translational research

In addition to considering how long a distinct medical entity that we would recognize as scleroderma has been recognized, it is useful to place the diagnosis and classification of scleroderma in a historical context. It is clear that there was initially some reluctance to group together all forms of the disease that we would recognize today, and this is perhaps reflective of the advances that have occurred in imaging and laboratory investigation and a greater appreciation of the link between different organ-based manifestations. The milestones in the history of scleroderma bear testimony to the gradual realization of the heterogeneity of the disorder. For a more detailed discussion of the fascinating history of this disease the reader is referred to the excellent historical review by Rodnan, the "father" of modern-day clinical scleroderma [1].

It is often considered that the first description of the systemic disease that we recognize as scleroderma was in 1753 by Cario Curzio (Naples Italy) (Fig. 1.1). However, a careful review of the reported case suggest the diagnosis may in reality have been *scleroedema* because of the distribution of the skin changes and due to an apparent improvement in the 17-year-old female patient after a combination of therapeutic endeavors that included bloodletting, warm milk, and small doses of elemental mercury. In 1836, Fantonetti (1791–l877), a Milanese physician, became the first to use the term *scleroderma* to designate a disease in an adult. However, it is likely that his patient also had scleroedema. The first convincing case of scleroderma was reported in 1842 and then several other cases were published prior to 1847, a year when interest in the disease greatly increased. By 1860 numerous cases had been reported and the first articles that attempted to review the disease were published. Maurice Raynaud (1834–1881) described a patient with *sclerodermie* and cold induced "asphyxie locale" – this was the first description of Raynaud phenomenon in scleroderma. Just as for scleroderma it has been speculated that the first cases of Raynaud phenomenon may have included individuals with an alternative diagnosis underlying their acrocyanosis and vascular insufficiency. Sir William Osler made the diagnosis of scleroderma while at the Johns Hopkins Hospital between 1891 and 1897. Osler appears to have clearly appreciated the systemic nature of the disease, and to recognize the enormous clinical burden that patients with scleroderma endured when he wrote: *In its more aggravated forms diffuse scleroderma is one of the most terrible of all human ills. Like Tithonous, to "whither slowly," and like him to be "beaten down and marred and wasted" until one is literally a mummy, encased in an ever-shrinking, slowly contracting skin of steel, is a fate not pictured in any tragedy, ancient or modern.* Matsui (Japan, 1924) further highlighted the importance of visceral involvement as based on several autopsies that he had performed in individuals that had succumbed to the disease. Goetz (Capetown, 1945) further confirmed the multisystem involvement and suggested the disease be named *progressive systemic sclerosis*. The qualifying term "progressive" was later considered to be inaccurate in some cases that either remained stable or improved, or has generally been dropped. It does however serve to highlight the potential severity

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J. Varga et al. (eds.), *Scleroderma: From Pathogenesis to Comprehensive Management*,
DOI 10.1007/978-1-4419-5774-0_1,

- Hippocrates and Galen described possible cases of scleroderma
- First convincing case published by Curzio (Italy) 1753

Treatment: "…warm milk, vapor baths, bleeding and small doses of quicksilver. After 11 months the patient's skin had become perfectly soft and flexible." A cure !?

- Scleroderma first established as a clinical entity, and called 'sclerodermie' by Gintrac 1847
- Raynaud's Phenomenon described 1852, and in 1871 associated with scleroderma
- Wollers 1892 " According to all observations, scleroderma does not appear to be a disease which threatens life directly." !! **But :**
- **Osler 1894 " .. patients are apt to succumb to pulmonary complaints or to nephritis."**

Fig. 1.1 Some of the key historic figures who contributed to the field of scleroderma are listed. Appreciation of the severity of the disease was confounded by clinical variability and absence of unifying diagnostic criteria or investigational modalities

of the worst forms of the disease. The potential importance of subtypes of scleroderma began in 1964, when Winterbauer reported cases with the CRST (calcinosis, Raynaud's phenomenon, sclerodactyly, and telangiectasias) syndrome. A similar group of patients was reported in 1920, named after the authors, the Thiberge-Weissenbach syndrome. Velayos and colleagues recognized that esophageal dysmotility was common in these patients; so now it is called the CREST syndrome. In 1969, 58 autopsy cases of scleroderma were compared with matched controls. The organs found to be frequently and significantly involved by this disease were the skin, gastrointestinal tract, lungs, kidneys, skeletal muscle, and pericardium. This report first described the systemic nature of vascular pathology in scleroderma with findings of both kidney and lung arterial changes. Rodnan introduced a clinical method to evaluate the extent of skin disease, and correlated this with skin biopsy weight and later with collagen content in the skin. From the same center in Pittsburgh, Steen, and Medsger and others did extensive surveys of large populations of scleroderma patients defining the clinical course and specific subtypes of disease. In the 1970s a subcommittee [2] of world experts established diagnostic criteria and Leroy [3] and colleagues suggested the classification of two major subsets of disease defined by skin involvement: *limited* and *diffuse*. Recent work by several investigators has recognized that scleroderma specific auto-antibodies occur that associate with subtypes of disease and can be used to predict disease course. Work in the modern era has revealed details of the pathogenesis of the disease and the recognition that scleroderma is a complex polygenetic autoimmune disease associated with a unique disease process involving tissue fibrosis. Although no drug is yet discovered that can be called a successful disease modifying agent that controls the underlying disease process, major progress has been made in managing specific organ disease. The discovery of that an angiotensin converting enzyme inhibitor could reverse the scleroderma renal crisis in the 1970s changed the course of kidney disease and improved the survival of patients. Current therapies for gastrointestinal, cardiac, pulmonary vascular and interstitial lung disease have improved quality of life and survival. There has been a growing interest in scleroderma around the world, and the emergence of specialist centers that now provide effective patient care and scientific interactions with each other and private industry to discover the causes and new treatment for scleroderma. Although uncommon and without effective disease modifying therapies the relevance of scleroderma to a broad range of other medical conditions is now fully appreciated and this has benefited management though translation of treatments into the organ based complications of scleroderma. In addition, scleroderma (Fig. 1.2) provides a potential platform for the development of anti-fibrotic or vascular therapies that could be beneficial in other commoner diseases that are characterized by vascular insufficiency or extracellular matrix overproduction.

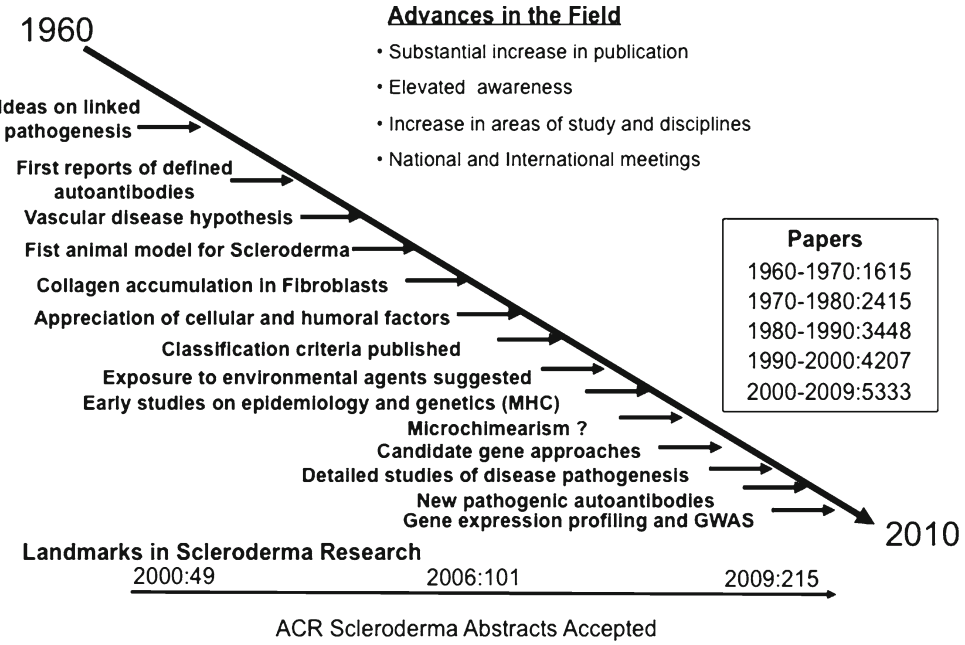

Fig. 1.2 The timeline of translational research (Fig. 1.2) into scleroderma illustrates the growing interest in the disease together with better appreciation of its complexity and more candidates for pathogenesis

Table 1.1 The landmarks in the history of scleroderma

Date	Person	History of scleroderma
c. 400 BC	Hippocrates	Described an Athenian with indurated unpinchable skin. Insufficient detail to ascertain whether this was scleroderma
1753	Curzio	Description of young woman of Naples with "excessive hardness of the skin" – possibly scleroderma, but probably scleroedema of Buschke
1847	Gintrac	First use of the name "sclérodermie"
1847	Forget	First description of joint involvement in scleroderma
1854	Addison	First description of linear scleroderma
1862	Raynaud	Description of "local asphyxia and symmetrical gangrene of the extremities"
1878	Weber	Coexistence of scleroderma and calcinosis noted
1892	Osler	Tendency for scleroderma patients to die of pulmonary or renal disease noted
1893	Hutchinson	Association of scleroderma and Raynaud's phenomeon noted
1903	Ehrmann	Association of scleroderma and dysphagia noted
1910	Thibierge and Weissenbach	"Rediscovery" of the coexistence of scleroderma and calcinosi0073
1924	Matsui	First clear description of visceral involvement, with sclerosis of lungs, gastrointestinal tract and kidneys
1943	Weiss	Clear description of myocardial involvement in scleroderma
1945	Goetz	Coined the term "progressive systemic sclerosis"
1964	Winterbauer	Described the CREST subset (calcinosis, Raynaud's, oesophagitis, sclerodactyly, and telangiectasia)
1980	Masi	Preliminary classification criteria for systemic sclerosis published
2001	Medsger LeRoy	Early-scleroderma criteria suggested for minimal skin disease

Some of the key events in the history of scleroderma are listed in Table 1.1. This provides an approximate time line that demonstrates the recent progress in understanding the disease but it is important to observe that the outcome of the disease in terms of mortality has substantially improved over the past 20 years and that this has come at a time when there is a much better and more complete appreciation of disease burden from non-lethal manifestations. Thus, many more scleroderma patients are now living with the disease than are dying from it and this raises its own important challenges that are considered in detail in the various sections and subsequent chapters of this textbook.

References

1. Rodnan GP, Benedek TG. An historical account of the study of progressive systemic sclerosis (diffuse scleroderma). Ann Intern Med. 1962;57:305–19.
2. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980;23(5):581–90.
3. LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28(7):1573–6.