Sjögren's Syndrome: Past, Present and Future

Robert I. Fox, M.D., Ph.D.
Chief, Rheumatology Division
Scripps-XiMED Medical Center
9850 Genesee Ave, #910
La Jolla, California 92037 USA

Carla M. Fox, R.N.
Scripps-XiMED Medical Center
Clinic Administrator

*Corresponding author: robertfoxmd@icloud.com

Key Words:

Sjögren, Henrik
medical history,
anti-SSA

Abstract

The tantalizing task of writing a chapter entitled *"Sjögren's Syndrome: Past, Present, and Future"* as an introduction to this clinical handbook recounts a journey that is now over a century old with no end in sight-- at least not in the foreseeable future.

Sjögren's Syndrome (SS) still remains one of our most challenging disorders to diagnose and manage. The transition from past to present is relatively easy, since there are many classic descriptions of Sjögren's Syndrome from the 1950's, and these pioneering publications list the pathology and clinical features that are virtually the same as we recognize today.

This chapter will also highlight some of the *diagnostic and therapeutic challenges* that we face at the present time. Furthermore, we hope to *point the directions that we must address in the future* to identify the underlying cause(s) and therapies that fundamentally improve the SS patient's quality of life.

Perspective

SS is a chronic autoimmune, rheumatic disorder most commonly characterized by *dryness of eyes and mouth* due to lymphocytic infiltration of the lacrimal and salivary glandular tissues. The condition has **"benign" features** that include *dryness* as well as *vague myalgias, fatigue and cognitive changes*. These features are still poorly understood and treated. The benign

symptoms represent the impact of the inflammatory process on the immune, neural, hormonal and vascular signals necessary for normal secretory function or cognitive processes.

In addition, SS patients have specific **extra-glandular manifestations** affecting: renal, pulmonary, neural (both central and peripheral), hematopoietic, lymphatic, cardiac, and gastro-intestinal systems [A].

Although *there are clear overlaps with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and scleroderma*, there also are clear differences (serologic, clinical, pathogenic) that distinguish these disorders.

It is worth noting the surprising finding that *the majority of patients with dry eyes due to SS were initially misclassified as either SLE or RA* in a multi-center study from excellent academic centers based largely on the finding of a positive Anti-Nuclear Antibody or rheumatoid factor [2].

This **initial mislabeling of SS patients** as another diagnosis:

- *deprives the patient of adequate follow-up* for their particular ocular and oral complications, as well as proper attention to the particular extra-glandular manifestations that SS patients develop.
- also hinders the enrollment in clinical trials of SS patients with significant extra-glandular manifestations who may benefit from biological therapies but may still be sitting in pulmonary, renal or hematology clinics undiagnosed or misdiagnosed.

Sjögren's has a worldwide distribution, and interestingly, *the genomic associations differ in distinct ethnic groups*, even though the histologic features of the tissue biopsies and epitopes recognized by autoantibodies show great similarities [3-5]. Comparison of genetic and non-genetic factors in these different groups may help find the common pathways important in clinical symptoms.

There are also important geographic differences that are associated with differences in clinical manifestations among different SS populations. For example, recent studies have shown that pulmonary hypertension (PAH) in Chinese and Korean cohorts is more prevalent in SS and SLE patients in these countries than in scleroderma patients. However, we have many Chinese and Korean SS patients in the US, and our registries do not reflect this shift in PAH incidence [6]. This type of comparison may lead the way to identifying environmental factors that trigger PAH in people of different genetic backgrounds.

Key Points

* Sjögren's is frequently misdiagnosed

* Genomic associations differ in different ethnic groups

* Geographic differences are associated with differences in the clinical

expression of the disease

BRIEF REVIEW OF THE PAST— as *"we only stand on the shoulders of past giants."*

Early History

The traditional paragraph on the "history" of SS starts with *Mikulicz* in 1892 describing a neck mass in a male with lymphocytic infiltrates and myoepithelial islands [10]. The term *"Mikulicz syndrome*" was used until the 1920's when it was subsequently discarded, since it failed to distinguish SS from other lymphocytic infiltrative processes such as tuberculosis and lymphoma [11]. Ironically, the recent recognition of the *IgG4 syndrome* (which occurs predominantly in males of this age and exactly parallels Mikulicz's description) suggests that the original view of SS and Mikulicz syndrome as "identical disorders" was indeed incorrect [12].

In retrospect, one of the earliest and most convincing descriptions of Sjögren's occurred on March 9, 1888 when a British physician, W. B Hadden presented a case to his colleagues at the Clinical Society of London (Figure 1). Dr. Hadden described a 65-year-old female who was admitted to the hospital with a 7-month history of progressive dry mouth associated with dysphagia and the need to constantly drink fluids. As Dr. Hadden related, two months earlier *"she had occasion to cry-- but no tears would come".*

On exam, the patient was well appearing and her vital signs were normal. The only notable finding was the mouth; he recounted that *"nearly all her teeth are wanting" and "the tongue is red, devoid of epithelium, and cracked in all directions like a crocodile's skin."*

The patient spent two weeks in the hospital for observation and other diagnostic measures of the day. Finally, at the conclusion of the observation period, the decision was made to treat her with a medicinal remedy (tincture of jaborandi) administered both orally and subcutaneously. The patient responded and continued this therapy as an outpatient. Interestingly, the active ingredient in tincture of jaborandi, pilocarpine, was FDA-approved in tablet form some 110 years later as the first prescription drug for Sjögren's known as Salagen®.

In 1933, an ophthalmologist named *HENRIK SJÖGREN described a constellation of ocular and oral dryness and arthritis in a large group of patients* as part of his ophthalmology doctoral thesis in Scandinavia [13].

This author had the honor to meet an elderly Dr. Sjögren shortly before his death, at the time of the first International Symposium on Sjogren's Syndrome in Denmark (Figure 2.) [14].

As an incentive to young researchers, it is important to note that Dr. Sjogren recounted how his thesis was given a poor grade, and he was banished from academia to a remote region of Scandinavia to practice ophthalmology. He was sustained during this "exile," and retained his "sanity" only by playing the piano until his early work was "rediscovered." This rediscovery occurred in a series of articles in the 1950's, beginning with a widely read *New England Journal Clinical Pathology* Conference by Drs. Morgan and Bloch [15, 16]. Of importance, the basic

clinical and pathologic features that we recognize today were clearly described in a study of 62 patients by Bloch et al in 1956. [15].

The Pioneers

In the *United States*, the next major steps in SS were presented in a large series of papers by Norman Talal et al. mainly during the 1960s and 1970s [17-24]. Equally as important, Talal trained an entire generation of postdoctoral fellows, initially at National Institutes of Health (NIH) and later in San Francisco where he worked closely with outstanding members of the dental school such as Greenspan and Daniels [25-27]. These former "post-doctoral fellows" and collaborators have formed the nucleus of SS research centers across the world including teams in Japan led by Sugai and Miyasaka[28], and Saito and Tsubota[29].

Talal also provided the scientific backing to the patient organization the Sjogren's Syndrome Foundation. Inc. (SSF), that allowed clinical recognition and validation of SS as a disease with significant morbidity, and the reception and input of SS patients into their unmet needs. Of course, other groups in the US were entering the field such as Provost [30], Tan and Reichlin (whose contributions are described below)— whose postdoctoral fellows would also establish a central network of SS care and research.

Meanwhile in *Europe*, outstanding groups of researchers were forming study groups and later research clinical centers of excellence for SS, including the groups lead by Jonnsen [31], Manthorpe and Oxholme [32, 33], Konntinen [34], Bombardieri and Vitali [35], and Tzioufas, Mavragani and Moutsopoulos [36].

In *India*, vibrant research sprang up in major cities under the direction of Sharma [37], Agrawal and Pandya [38].

In *China*, centers of excellence were established by Chen [39], Dong Yi and Zhang [40], and expanded by Guo [41]. As a tribute to these leaders, each of these centers has remained a leading center of SS clinical practice and research.

Although many other pioneers have not been listed above, the point is that a vibrant community of SS clinical and research excellence has been "seeded" by these leaders and is now ready to flourish with new approaches and new vitality.

Looking Backward at the SS-A and SS-B Autoantigens

The examination of autoantibodies and cloning of autoantigens relevant to SS was first performed by Tan in San Diego [42, 43] and Reichlin (in Buffalo and later Oklahoma) [44, 45] mostly during the 1980's. His team used a technique called immunodiffusion with serum from patients who had initials "Ro" or "La." Although Dr. Reichlin really made the first association of "Ro" and "La" antibodies and particular HLA-DR genes in both SLE and SS patients, the work

of Tan and the more powerful national autoantibody reference center at The Scripps Research Institute (TSRI) in San Diego led to our current use of the nomenclature “Sjögren's Syndrome-associated antigen, SS-A. The antibody recognizes an antigen which is actually composed of two different proteins of size 60 Kd and 52 Kd and RNA. (Full disclosure requires that I identify that Eng Tan was my Chairman upon my arrival at Scripps.) Dr. Tan and his team would use these autoantibodies to “clone” the relevant cellular antigen using a technique called phage display library.

Two interesting findings emerged quickly. First, the human autoantibodies were often directed at the active or binding site of the host protein. This is illustrated below where the antibody would bind at the same site where a virus might “find a home” and may have been a way for the cell to protect itself.

Also, the particular autoantigens invariably possessed an unusual amino acid sequence such that they could resist the normal proteolytic digestion that comes with cell death (necrosis or apoptosis). In cellular terms, this meant that they lacked “caspase enzyme digestion sites” and could remain stably on the dying cell’s surface in an “apoptotic” bleb. Also, this resilience of the autoantigen and its ability to bind to the chaperone molecule (which contained single and double stranded RNA sequences) made it an ideal molecule to start a vicious cycle of autoimmunity in a person with the correct genetic predisposition (i.e. HLA-DR sequence).

Since a great deal of attention in the diagnostic criteria and pathogenesis are paid to “antibodies to SS-A antigen and its antibodies,” it is worth a brief note to outline the history of this important cellular protein and its normal role.

In 1983, striking similarities were noted between an adenovirus associated RNA (VAI and VAII) and two small Epstein-Barr Virus encoded RNA’s transcribed by RNA polymerase III. All of these viral RNA’s were “non-coding,” but found to co-precipitate with the anti-La protein [46] from SLE sera [47]. The Ro and La antigens were felt to bind to a tRNA-like structure that belonged to a family called hYRNA and serve as molecular chaperones.

Similarly, to the Victorian chaperone, a molecular chaperone escorted the relevant RNA to the correct and intended location within the cell, while protecting it from “degrading” circumstances. These chaperones also play a role in control of transcription of DNA by interaction with chromatin and other initiation factors.

In patients who are genetically predisposed-- with a series of genes that regulate antibody production (particularly HLA-DR antigens and interferon regulatory genes), an antibody to SS-A may be present in “asymptomatic” individuals for many years prior to any clinically detectable SS [48].

However, other ***genetic as well as environmental factors*** *are also important for clinical disease expression* [48]. For example in an early study of identical twins by Reichlin, only 3/7

SS-A positive twins both developed autoimmunity (i.e., concordance), while 4/7 remained normal during a 15 year follow-up (discordant for SLE or SS) [49].

Similarly, a majority of SS-A positive females who had fetuses with SS-A-related neonatal heart block did not develop SS [50] during many years of follow-up. Given other hormonal factors and the microenvironment of the salivary or lacrimal glands (which are rich in growth factors and neural stimulatory signals), a self-perpetuating cycle of inflammation requires additional stimuli to develop and paralyze glandular function. Further, these results instruct us that ***the finding of an antibody to SS-A in clinical screening does not always equate to a diagnosis of SS***.

Key Points

* Anti-SSA/SSB recognize antigens that act as molecular chaperones for RNA and play a role in DNA transcription

* Genetic and environmental factors play a role in the enteropathogenesis of SS

* Not every anti-SSA positive patient will develop Sjögren's syndrome

QUESTIONS FOR THE PRESENT

Classification and Diagnosis

In the "present" section of this introductory chapter, an important advance to emphasize has been the recent improvements in the classification criteria for SS [1] that are necessary for basic research, clinical trials by industry and designation of endpoints by FDA regulators. These criteria and the guidelines for diagnostic testing suggested by both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) are the subjects of chapter 2 in this book.

Despite these achievements, however, it is recognized that further modifications of these criteria will be required in the future, and subsets of patients with SS will likely need to be defined by genetic markers, other biomarkers, or other modalities such as ultrasonography.

In recent years, recruitment for clinical trials has led to increased awareness of SS among both physicians and patients. The aforementioned guidelines were developed to facilitate the identification of uniform groups of patients for research trials but by default are frequently used as diagnostic criteria by clinicians as well.

However, in practice, **rheumatologists rarely get minor salivary gland biopsies** [2], and both university and community pathologists rarely interpret them according to uniform guidelines [B}. **This has led to an excessive reliance on the antibody to SS-A as a diagnostic test, and a lack of understanding of the variables surrounding both false-positive and false-negative antibody tests.**

We know that **a large subset of SS patients (about 1 in 3) will be seronegative, and that failure to biopsy in this group will miss diagnoses**.

Conversely, based on population studies, **false positive antibodies to the SS-A antigen also exist, and many of these individuals will not develop SS**.

Additionally, other autoantibodies are described in SS that have diagnostic or prognostic value but not routinely tested. For example, patients with antibodies that recognize the centromere-c antigen (anti-centromere antibodies) may exhibit *some features of limited scleroderma* in addition to SS, including an *increased prevalence of Raynaud's phenomenon*, and these antibodies may occur in up to 13% of SS patients [7].

Clinical Trials

The present is also dominated by numerous "failed" clinical trials. But it is not really fair to say the results represent true failure. In recent studies of biological therapies, for example, we have lumped subjects with "benign" and "extra-glandular" manifestations into a single group hoping to find differences after treatment in single or composite endpoints with the goal of obtaining eventual FDA approval. The majority of SS patients enrolled in these studies do not have extra-glandular disease, and thus, the cohort is dominated by patients with "benign" symptoms. In a world of "personalized" medicine, we must evaluate particular manifestations and their response to therapy. By analogy, treatments for diabetic neuropathy approved by the FDA do not require that the underlying problem of diabetes or its multiple symptoms be eliminated.

Of note, all of the medications approved for SS to date have been studied with the focus on SS as a ***"single organ"*** disease.

Etiology and Pathogenesis

Although the essential clinical features of SS (including its spectrum of autoantibodies and pathology) were outlined by Bloch et al in 1953, **we still really do not understand the underlying cause of SS**.

Its epidemiologic pattern suggests that *both genetic and non-genetic factors (e.g. environmental or epigenetic modifications) play a role*. Additionally, since SS is largely a disease of women, *hormonal factors and Toll receptors (located on X chromosome)* must also be important. The bimodal age of expression suggests the importance of hormonal changes that act either directly or indirectly on the normal processes of failed "tolerance" that characterize autoimmune diseases.

A common misconception is that the dryness of SS results entirely from destruction of the glands. Although parenchymal loss from apoptosis of glandular epithelial cells plays a role, histologic studies by thought leaders such as Roland Jonnson and Konntinen et al [56-58]

showed that *even* ***in patients with little or no saliva production, the majority of ductal/acinar structures as well as their innervation remain detectable.***

Apparently, *the inflammatory microenvironment of cytokines and metalloproteinases prevents the orientation and functional activity of the residual secretory glands* [55, 59]. Thus, glandular function depends on the temporal integration of neural and vascular signals in a precise pattern that can lead to secretory function [59].

In ophthalmology, the importance of a "functional circuit" that links the unmyelinated afferents that go to the lacrimal nucleus in cranial nerve V, and then, subsequently, to the various parts of the cerebral cortex, is a relatively new concept described by Stern et al [51, 52]. The components of the tear film and its stability were elaborated by Pflugfelder [53] and Dartt [54, 55] who emphasized the additional role of glands. The recognition that we must look at the entire "functional unit" as a goal for the future is really setting the "holy grail" for the next decade of dry eye research and may be applicable to other aspects of the disease. This approach should help us better understand the interface of the immune system, neural system and hypothalamic axis.

Clinical Challenges

There is a diminutive sound to the term "benign" symptoms in SS as ***patients still struggle with dry eyes and dry mouth*** (see chapters 3 and 4), **and both of these symptoms can significantly compromise quality of life**.

Dry eye symptoms continue to be the most common cause of patient distress in SS, and **dry/painful eyes are now the most common cause for visits to ophthalmologists in the US** and UK [60, 61]. The cost in medical evaluations and the myriad of over-the-counter "moisturizing" eye drops filling multiple pharmacy shelves reflects the scope of this problem and accounts for well over $175 billion dollars in annual sales [61]. Medical economic analysis has recently recognized that being unable to fully participate at the workplace (a term called **lack of *"presentness"***) has a real cost over 5 times the cost of absenteeism [62].

We live in an era where patients increasingly work at computers ***(screen activity drops blink rate by 90% and greatly exacerbates dry eye)*** in highly air conditioned (low humidity) environments, and deal with increasing stress related to economic factors, thus, further decreasing secretory function by adrenergic antagonism of cholinergic inputs.

Therefore, we should not be surprised by the "silent epidemic" that pervades ophthalmology clinics, where ocular discomfort remains among the most common reasons for patient referrals.

In volumes such as this, rheumatologists and other providers are being educated to help SS patients deal with eye discomfort (see chapter 4) and are learning new terms such as *"**tear film instability**"* and *"**meibomian gland dysfunction**."* These conditions must be treated before other ocular lubricants or inflammatory drops can fully work.

Since many rheumatologists will eventually assume the role of primary care provider for SS patients, this is especially important, as not every ophthalmologist or optometrist in the community is interested in dry eyes.

Similarly, ***dry mouth*** *and its various health consequences continue to impact patients' overall condition*. This problem negatively impacts the patient's *nutrition* (as they turn to "soft foods" high in sugar content), as well as *socialization*, and may lead to chronic anxiety, isolation, depression and despair.

The SS patient, in frustration, often turns to the Internet (that has become a citadel of misinformation), and sometimes succumbs to SS blogs and misleading "official SS"-appearing websites merchandising "cures" and worthless products. Systemic therapies for dryness are currently available but limited by cholinergic side effects. Over-the-counter remedies are costly, time consuming to use, and only provide transient relief at best. Clearly better treatments are needed.

Patients may also complain to their rheumatologists of ***burning mouth*** **and a "flare" of other symptoms** in certain clinical situations. This scenario often occurs after treatment of a sinus or other infection by the primary care physician with antibiotics. This predisposes to the overgrowth of Candida species in the oral cavity and triggers mouth burning, increased oral discomfort and decreased oral intake. Stomatopyrosis makes eating unpleasant and further compromises the patient's nutritional status and quality of life. It therefore behooves each and every provider to recognize the signs and symptoms of acute or chronic erythematous candidiasis which frequently occurs as a complication of SS but can be easily managed (chapter 3).

One of the most devastating and costly oral complications of SS is accelerated caries. Sjögren's syndrome patients have more caries, tooth extractions, and higher dental expenses over a lifetime compared to healthy controls (D,E).

Surprisingly, many Sjögren's patients, at the time of initial evaluation, receive little attention to this problem even by dental professionals. However, prevention of oral caries needs to become a full-time preoccupation for patients and a major priority for the dentist or oral medicine specialist, rheumatologist and other members of the care team. The SSF has now published clinical practice guidelines for caries prophylaxis, thus, emphasizing the importance of this problem and providing a treatment algorithm to follow right now [F]. Further research to more precisely define the risk factors for caries is desperately needed.

Consideration of current research in SS will reveal that the "present" is largely dominated by studies on genomics, transcriptomics, and mechanisms of disease. The discoveries that may come from this work will undoubtedly provide the foundation for more targeted therapies in the future, the advent of personalized medicine in SS and, perhaps even a cure.

Key Points

* Sjögren's patient who are dry often have intact salivary glands suggesting other mechanisms for dryness besides tissue loss from apoptosis

* Dry eyes and dry mouth are not trivial and can significantly impair quality of life

* Sjögren's sufferers continue to have many unmet needs

LOOKING FORWARD

Early Diagnosis

In terms of future directions, better education of primary care physicians and other specialists on the proper use and interpretation of serologic tests would have an immediate impact on diagnostic accuracy. Given the fact that Anti-SSA positivity is frequently detected in anti-nuclear antibody (ANA) negative SS patients, proper screening for Sjögren's would be best performed using a panel (ANA, anti-SSA/SSB).

*Providers should also embrace the concept of a **comprehensive, multidisciplinary approach** to the evaluation of SS for every patient in order to ensure a systematic and thoughtful assessment that yields a timely diagnosis.*

This is especially important when considering Sjögren's as a diagnosis in patients who present with extraglandular manifestations, because at the time of initial evaluation, sicca symptoms in this group are frequently minimal or nil.

Since the correlation between the severity of ocular and oral symptoms and the results of objective tests for dry eyes and dry mouth is often poor [G,H], the clinician is always justified in pursuing the full diagnostic workup in the appropriate clinical situation even in the absence of sicca symptoms.

Precision Medicine and Unmet Needs

In the era of precision medicine, it's time to use a ***personalized medicine approach*** for SS and recognize that a variety of therapies such as ***rituximab, abatacept*** and other treatments have indeed proven efficacious for extraglandular manifestations in certain SS patients [I]. The "one size fits all approach" to SS therapeutics has hindered care and should be abandoned.

Future advances in pharmacogenomics, epigenetics, cytokine research or the discovery of other novel biomarkers will allow us to match specific therapies to specific patients, and lead to more cost-effective utilization of resources, and hopefully, greater availability of these treatments to SS patients down the road. Developments in this field should be greatly accelerated by the use of **"artificial intelligence."** Additionally, more clinical practice guidelines

from the SSF and other organizations should also be available to guide our therapeutic strategies.

A **personalized medicine approach** will also better focus our attention on the many unmet needs of this population. More aggressive treatment of "benign" and highly prevalent manifestations such as dry eyes, dry mouth, fatigue and cognitive changes will not only significantly improve patient quality of life-- but also lower medical and dental costs related to common long-term complications.

The classification and treatment of neurological signs and symptoms (both central and peripheral) (chapters 9-10) as well as lymphoproliferative manifestations (chapter 8) also remain significant challenges. In this future direction, *we will need to gain a better understanding of the interface of the various immune, endocrine, and neurological factors that contribute to the pathogenesis of SS*, in order to successfully meet these goals. A multidisciplinary approach to the development of specific treatments for specific symptoms will drive this process.

The full realization of precision medicine will be further accelerated by progress in **genetic studies,** and with the use of **artificial intelligence**, also enable future risk profiling for life-threatening complications (see chapters 6-10). For example, the recent discovery of an association between mutations of the A20/TNFAIP3 gene and the development of mucosa associated lymphoid tissue marginal zone B-cell lymphomas [J] in SS will undoubtedly stimulate more research in this area and may lead in the future to the first screening tests for lymphomas in SS.

Clinical Trials

Advances in SS research using DNA and RNA sequencing [8] have already revealed fascinating cytokine and chemokine mechanisms that are associated with extraglandular manifestations, and have led to an expanded panel of therapeutic targets in SS.

We must therefore continue concerted efforts to develop novel therapeutics for SS including biological therapies that can safely halt the progression of the disease and/or prevent lymphoproliferation and its life-threatening complications (chapters 6,8). Clinical trial results of immunomodulating therapies have yielded disappointing results thus far. However, once the first agent is FDA approved the floodgates will open.

Interdisciplinary Care and Future Directions

Until a cure for SS is discovered, improved interdisciplinary cooperation with ophthalmology, oral medicine, neurology and other specialists should be pursued to establish a multi-specialty framework for improved care. When considering the complexity of problems that these patients

face, it would also seem logical to ask the rheumatologist to assist the family doctor in the role of primary care provider. Further reimbursement from healthcare insurers for cognitive services and coordination of care would help this model to flourish.

In moving forward, *we also need to consider new paradigms of pathogenesis*. Perhaps we should view the immune system as the body's *"sixth sense,"* as it sends lymphocytes out to the periphery to sense viral infections or apoptotic debris.

We know that lymphocytes possess a full repertoire of neural actions, and an important part of the immune function may be to report back to the brain about the "situation in the remote provinces."

Furthermore, since the patterns of cortical distribution of visual and oral signals have now been validated and biologically mapped, further study of the central nervous system may provide additional insight for a better understanding of key patient problems.

Through the millennium of Darwinian evolution, the importance of vision and taste have selected the neural and vascular innervation of the eye and mouth. Exploring this relationship may provide the key to unlocking many Sjögren's mysteries.

This intriguing book engages the expertise of multiple authors from various disciplines to define the most significant clinical problems in Sjögren's and provides practical up-to-date advice to guide providers on management.

More importantly, it extends the dialogue between multiple medical subspecialists, basic researchers, pathologists and oral medicine specialists, all of whom contribute to the care of these patients. It also provides a basic vocabulary as we move into a most exciting next decade where we expect to see significant advances in our knowledge of the pathogenesis, epidemiology and treatment of SS using a multi-disciplinary research approach.

Key points

* Multidisciplinary care and a "precision medicine" approach are needed

* Understanding SS requires a better understanding of the interaction between the immune system and neuro-endocrine pathways

Conclusions

The origins of Sjögren's syndrome in Western medicine date back to the late 19th century, and concepts regarding etiology and pathogenesis continue to evolve. Despite the discovery of

marker autoantibodies for SS in the 1980's and, more recent improvements in classification criteria, the identification of Sjögren's in early stages of the disease remains quite challenging.

Progress in therapeutics has lagged even further behind, and there are currently many unmet clinical needs. A greater emphasis on a *multidisciplinary approach* toward diagnosis and management and the advent of *personalized medicine* will significantly impact patient care. Ultimately, better stratification of patient subsets by biomarkers and a greater understanding of the interplay between the immune system, neuroendocrine, and other disease mechanisms will facilitate the future development of more targeted therapies and, perhaps, one day…
even a CURE.

References

1. Shiboski, C.H., et al., *2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts.* Arthritis & Rheumatology, 2017. **69**(1): p. 35-45.
2. Rasmussen, A., et al., *Previous diagnosis of Sjögren's Syndrome as rheumatoid arthritis or systemic lupus erythematosus.* Rheumatology, 2016. **55**(7): p. 1195-1201.
3. Taylor, K.E., et al., *Genome-Wide Association Analysis Reveals Genetic Heterogeneity of Sjögren's Syndrome According to Ancestry.* Arthritis & Rheumatology, 2017. **69**(6): p. 1294-1305.
4. Fei, H., et al., *The genotyping of the HLA-D region and specific RFLP patterns for Chinese Han Population.* Chinese J of Genetics, 1994. **20**: p. 75-85.
5. Kang, H.-I., et al., *Comparison of HLA class II genes in Caucasoid, Chinese, and Japanese patients with primary Sjögren's syndrome.* J. Immunol., 1993. **150**: p. 3615-3623.
6. Fox, R., *The incidence of pulmonary hypertension is higher in systemic lupus and Sjögren's patients than in scleroderma patients in China*. 2018, SAGE Publications Sage UK: London, England.
7. Gelber, A.C., et al., *Distinct recognition of antibodies to centromere proteins in primary Sjögren's syndrome compared with limited scleroderma.* Annals of the rheumatic diseases, 2006. **65**(8): p. 1028-1032.
8. Altorok, N., et al., *Genome-Wide DNA Methylation Patterns in Naive CD4+ T Cells From Patients With Primary Sjögren's Syndrome.* Arthritis & rheumatology, 2014. **66**(3): p. 731-739.
9. Bombardieri, M., et al., *Meeting report Highlights of the 14th International Symposium on Sjögren's Syndrome.* Clin Exp Rheumatol, 2018. **36**(112): p. S3-S13.
10. Mikulicz, J.H., *Uber eine eigenartige symmetrische Erkrankung der Tranen- und Mundspeicheldrusen.*, in *Beitr. Chir. Fortschr.*, G.T. Billroth, Editor. 1892: Stuttgart. p. 610-630.
11. Morgan, W.S., *The probable systemic nature of Mikulicz's disease and its relation to Sjögren's syndrome.* N. Eng. J. Med., 1954. **251**: p. 5-9.
12. Stone, J.H., Y. Zen, and V. Deshpande, *IgG4-related disease.* New England Journal of Medicine, 2012. **366**(6): p. 539-551.
13. Sjögren, H.S., *Zur kenntnis der keratoconjunctvitis sicca (Keratitis folliformis bei hypofunktion der tranendrusen).* Acta Opthalmol (Copenh), 1933. **2**: p. 1-151.
14. MANTHORPE, R., et al., *PROCEEDINGS OF 1ST INTERNATIONAL SEMINAR ON SJOGRENS-SYNDROME 1986, COPENHAGEN, MAY, 1986-FOREWORD*. 1986, SCANDINAVIAN UNIVERSITY PRESS PO BOX 2959 TOYEN, JOURNAL DIVISION CUSTOMER SERVICE, N-0608 OSLO, NORWAY.
15. Bloch, K.J., et al., *Sjögren's syndrome: A clinical, pathological and serological study of 62 cases.* Medicine (Baltimore), 1956. **44**: p. 187-231.
16. Morgan, W.S., *The probable systemic nature of Mikulicz's disease and its relation to Sjögren's syndrome.* New England Journal of Medicine, 1954. **251**(1): p. 5-10.

17. Talal, N., *Sjogren syndrome and pseudolymphoma.* Hosp Pract (Off Ed), 1988. **23**(9A): p. 71-5, 78-80.
18. Talal, N., R. Asofsky, and P. Lightbody, *Immunoglobulin synthesis by salivary gland lymphoid cells in Sjögren's syndrome.* J. Clin. Invest., 1979. **19**: p. 19.
19. Daniels, T.E., et al., *The oral component of Sjögren's syndrome.* Oral Surg., 1975. **39**: p. 875-885.
20. Anderson, L.G. and N. Talal, *The spectrum of benign to malignant lymphoproliferation in Sjogren's syndrome.* Clin Exp Immunol, 1972. **10**(2): p. 199-221.
21. KALTREIDER, H.B. and N. TALAL, *The Neuropathy of Sjögren's SyndromeTrigeminal Nerve Involvement.* Annals of internal medicine, 1969. **70**(4): p. 751-762.
22. Talal, N., E. Zisman, and P. Schur, *Renal tubular acidosis, glom,erulonephritis and immunologic factors in Sjögren's syndrome.* Arthritis Rheum., 1968. **11**: p. 774-780.
23. Talal, N., L. Sokoloff, and B. W., *Extrasalivary lymphoid abnormalities in Sjögren's syndrome.* Am. J. Med., 1967. **43**: p. 50-55.
24. Talal, N. and J. Bunim, *The development of malignant lymphoma in Sjogren's syndrome.* Am. J. Med., 1964. **36**: p. 529.
25. Daniels, T.E., et al., *An evaluation of salivary scintigraphy in Sjögren's syndrome.* Arthritis and Rheumatism, 1979. **22**: p. 809-814.
26. Greenspan, J., et al., *The histopathology of Sjögren's syndrome in labial biopsies.* Age Aging, 1974. **1**: p. 197-201.
27. Cremer, N., et al., *Immunological and virological studies of cultured labial biopsy cells from patients with Sjögren's syndrome.* Clin. Exp. Immunol., 1974. **18**: p. 213-224.
28. Ogawa, N., et al., *Involvement of the interferon-γ–induced T cell–attracting chemokines, interferon-γ–inducible 10-kd protein (CXCL10) and monokine induced by interferon-γ (CXCL9), in the salivary gland lesions of patients with Sjögren's syndrome.* Arthritis & Rheumatism, 2002. **46**(10): p. 2730-2741.
29. Tsubota, K., et al., *Decreased reflex tearing is associated with lymphocytic infiltration in lacrimal glands.* J Rheumatol, 1996. **23**(2): p. 313-20.
30. Alexander, G.E., et al., *Sjögren syndrome Central nervous system manifestations.* Neurology, 1981. **31**(11): p. 1391-1391.
31. Jonsson, R., U. Kroneld, and A. Tarkowski, *Histological and functional features of salivary glands in rheumatic patients with oral sicca symptoms.* Scandinavian journal of rheumatology, 1988. **17**(5): p. 387-391.
32. Oxholm, P., et al., *Sjogren's syndrome: terminology.* Clin Exp Rheumatol, 1995. **13**(6): p. 693-6.
33. Frost-Larsen, K., Isager, H., and Manthorpe, R, *Sjogren syndrome treated with kGBromhexine A; a randomized clinical study.* Br. Med. J., 1978(1): p. 1579-1584.
34. Konttinen, Y.T., et al., *Neutral endopeptidase (EC 3.4.24.11) in labial salivary glands in healthy controls and in patients with Sjogren's syndrome.* Ann Rheum Dis, 1996. **55**(8): p. 513-9.
35. Vitali, C., et al., *Preliminary criteria for the classification of Sjögren's syndrome.* Arthritis & Rheum, 1993. **36**: p. 340-347.
36. Pavlidis, N., J. Karsh, and H. Moutsopoulos, *The clinical picture of primary Sjogren's syndrome: a retrospective study.* 1982.
37. Sandhya, P., et al., *AB0188 Systematic Analysis of the Oral Microbiome in Primary SjÖgren's Syndrome Suggest Enrichment of Distinct Microbes.* Annals of the Rheumatic Diseases, 2015. **74**: p. 953.
38. Agrawal, S., et al., *IL1RN* 2 allele of IL-1receptor antagonist VNTR polymorphism is associated with susceptibility to anklyosing spondylitis in Indian patients.* Clinical rheumatology, 2008. **27**(5): p. 573-576.

39. Fox, R.I., et al., *Expression of a cross reactive idiotype on rheumatoid factor in patients with Sjögren's syndrome.* J Immunol, 1986. **136**: p. 477-483.
40. Zhang, N. and Y. Dong, *Primary Sjögren's Syndrome in the People's Republic of China*, in *Sjögren's Syndrome*. 1987, Springer. p. 55-60.
41. Griffith, K., et al., *Molecular cloning of a novel 97 kd golgi complex autoantigen associated with sjogren's syndrome.* arth rheum, 1997. **40**: p. 1693-1700.
42. Chan, E.K.L., et al., *Sjögren's syndrome nuclear antigen B (La): cDNA cloning, structural domains, and autoepitopes.* J Autoimmunity, 1989. **2**: p. 321-327.
43. Martinez-Lavin, M., J. Vaughan, and E. Tan, *Autoantibodies and the spectrum of Sjögren's syndrome.* Ann Intern Med, 1979. **91**: p. 185-190.
44. Wasicek, C. and M. Reichlin, *Clinical and serological differences between systemic lupus erythematosus patients with antibodies to Ro versus patients with antibodies to Ro and La.* The Journal of clinical investigation, 1982. **69**(4): p. 835-843.
45. Provost, T.T., et al., *Ro (SS-A) positive Sjogren's/lupus erythematosus (SC/LE) overlap patients are associated with the HLA-DR3 and/or DRw6 phenotypes.* Journal of investigative dermatology, 1988. **91**(4).
46. Rosa, M.D., et al., *Striking similarities are exhibited by two small Epstein-Barr virus-encoded ribonucleic acids and the adenovirus-associated ribonucleic acids VAI and VAII.* Molecular and cellular biology, 1981. **1**(9): p. 785-796.
47. Moss, W.N. and J.A. Steitz, *Genome-wide analyses of Epstein-Barr virus reveal conserved RNA structures and a novel stable intronic sequence RNA.* BMC genomics, 2013. **14**(1): p. 543.
48. Jonsson, R., et al., *Autoantibodies present before symptom onset in primary Sjögren syndrome.* Jama, 2013. **310**(17): p. 1854-1855.
49. Reichlin, M., J. Harley, and M. Lockshin, *Serologic studies of monozygotic twins with systemic lupus erythematosus.* Arthritis & Rheumatism, 1992. **35**(4): p. 457-464.
50. Waltuck, J. and J.P. Buyon, *Autoantibody-associated congenital heart block: outcome in mothers and children.* Ann Intern Med, 1994. **120**(7): p. 544-51.
51. Stern, M.E., et al., *Conjunctival T-cell subpopulations in Sjogren's and non-Sjogren's patients with dry eye.* Invest Ophthalmol Vis Sci, 2002. **43**(8): p. 2609-14.
52. Fox, R.I. and M. Stern, *Sjogren's syndrome: mechanisms of pathogenesis involve interaction of immune and neurosecretory systems.* Scand J Rheumatol Suppl, 2002(116): p. 3-13.
53. Pflugfelder, S.C., et al., *Conjunctival cytologic features of primary Sjogren's syndrome.* Ophthalmology, 1990. **97**(8): p. 985-91.
54. Contreras-Ruiz, L., et al., *Modulation of conjunctival goblet cell function by inflammatory cytokines.* Mediators of inflammation, 2013. **2013**.
55. Zoukhri, D., R.R. Hodges, and D.A. Dartt, *Lacrimal gland innervation is not altered with the onset and progression of disease in a murine model of Sjögren's syndrome.* Clinical immunology and immunopathology, 1998. **89**(2): p. 126-133.
56. Tornwall, J., et al., *Distribution of vasoactive intestinal peptide (VIP) and its binding sites in labial salivary glands in Sjogren's syndrome and in normal controls.* Clin Exp Rheumatol, 1994. **12**(3): p. 287-92.
57. Konttinen, Y.T., et al., *Topology of innervation of labial salivary glands by protein gene product 9.5 and synaptophysin immunoreactive nerves in patients with Sjogren's syndrome.* The Journal of rheumatology, 1992. **19**(1): p. 30-37.
58. Konttinen, Y.T., et al., *Peptide-containing nerves in labial salivary glands in Sjögren's syndrome.* Arthritis Rheum, 1992. **35**: p. 815-820.
59. Konttinen, Y.T., et al., *Abnormal distribution of aquaporin-5 in salivary glands in the NOD mouse model for Sjogren's syndrome.* J Rheumatol, 2005. **32**(6): p. 1071-5.

60. Pflugfelder, S.C., *Prevalence, burden, and pharmacoeconomics of dry eye disease.* Am J Manag Care, 2008. **14**(3 Suppl): p. S102-S106.
61. Reddy P, Grad O, Rajagopalan K, The economic burden of dry eye: a conceptual framework and preliminary assessment. *Cornea,* 2004;23(8): 751-761.
62. Yao, W. and Q. Le, *Social-economic analysis of patients with Sjogren's syndrome dry eye in East China: a cross-sectional study.* BMC ophthalmology, 2018. **18**(1): p. 23.

A. Fox R, Extraglandular manifestations of Sjogren's syndrome (SS): dermatologic, arthritis, endocrine, pulmonary, cardiovascular, gastroenterology, renal, urology, and gynecologic manifestations. Sjogren's Syndrome: Practical Guidelines to Diagnoses and Therapy (R. Fox, C. Fox eds) 2011. Springer, New York City, NY.

B. Hadden WB. On "Dry Mouth," or Suppression of the Salivary and Buccal Secretions., *Transactions of the Clinical Society of London.* Longmans, Green and Co. London1888; Volume the 21st:*176-179.*

C. Vivino FB, Gala I, Hermann GA, Change in final diagnosis on second evaluation of labial minor salary gland biopsies, *J Rheumatol* . 2002 May :29(5): 938-944.

D. Christensen L, Petersen PE, Thorn JJ, Schiødt M. Dental caries and dental health behavior of patients with primary Sjögren syndrome. *Acta Odontol Scand.* 2001 Jun; 59(3):116-20.

E. Fox P, Bowman S, Segal B, Vivino F, Murukutla N, Choueiri K, Ogale S, McLean L. Oral involvement in primary Sjögren's syndrome. *J Am Dent Assoc*. 2008; 139(12): 1592-1601.

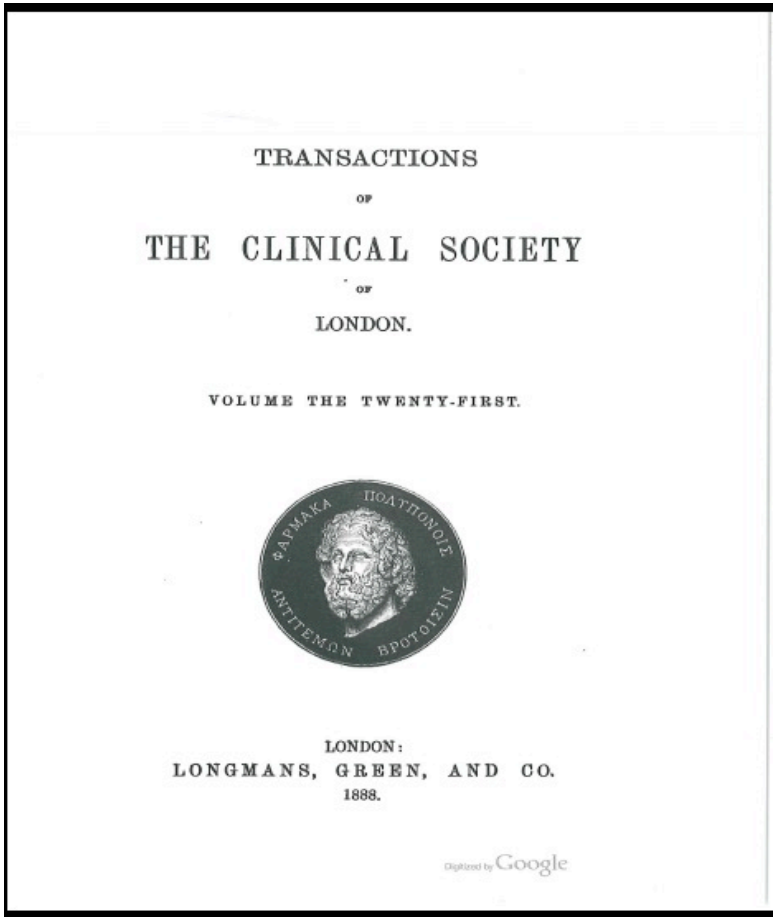
F. Zero T, Brennan M, Daniels T, Papas A, Stewart C, Pinto A, Al-Hashimi I, Navazesh M, Rhodus N, Sciubba J, Singh M, Wu A, Frantsve-Hawley J, Tracy S, Fox P, Lawrence Ford T, Cohen S, Vivino F, Hammitt K for the Sjogren's Syndrome Foundation Clinical Practice Guidelines Committee. Clinical practice guidelines for oral management of Sjogren disease: Dental caries prevention. *JADA.* 2016 Apr;147(4): 295-305.

G. Sullivan B, low Crews L,Messmer Foulks G, Nichols K, Baenninger P,Geerling G, Figueiredo F, Lemp M. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. *Acta Ophthalmol*. 2014: 92: 161–166.

H. Shiboski S, Shiboski C, Criswell L, Baer A, Challacombe S, Lanfranchi,H,. Schiodt M, Umehara H, Vivino F, Zhao Y, Dong Y, Greenspan D, Heidenreich A,Helin P, Kirkham B,, Kitagawa K, Larkin G, Li M, Lietman T, Lindegaard J, McNamara N, Sack K, Shirlaw P, Sugai S, Vollenweider C, Whitcher J, Wu A, Zhang S, Zhang W, Geenspan J, Daniels T. . American College of Rheumatology Classification Criteria for Sjogren's syndrome, a data driven, expert consensus approach in the Sjogren's international collaborative clinical alliance cohort, *Arthritis Care Res.* 2012;64 (4): 475-487.

I. S. Carsons, F. Vivino, A. Parke, N. Carteron, V. Sankar, R. Brasington, M.T. Brennan,W. Ehlers, R. Fox, H. Scofield, K.M. Hammitt, J. Birnbaum, S. Kassan, S. Mandel, Treatment guidelines for rheumatologic manifestations of Sjogren's: use of biologics, management of fatigue, and inflammatory musculoskeletal pain, *Arthritis Care Res.*2017;89 (4): 517–527.

J. Nocturne G, Boudaoud S, Miceli-Richard C, Viengchareun S, Lazure T, Nititham J, Taylor KE, Ma A, Busato F, Melki J, Lessard CJ, Sivils KL, Dubost JJ, Hachulla E, Gottenberg JE, Lombès M, Tost J, Criswell LA, Mariette X. Germline and somatic genetic variations of TNFAIP3 in lymphoma complicating primary Sjogren's syndrome. *Blood*. 2013 Dec 12;122(25):4068-76.



TRANSACTIONS

OF

THE CLINICAL SOCIETY

OF

LONDON.

VOLUME THE TWENTY-FIRST.

LONDON:
LONGMANS, GREEN, AND CO.
1888.

Digitized by Google

XXXVI.—*On "Dry Mouth," or Suppression of the Salivary and Buccal Secretions.* By W. B. Hadden, M.D. *Read March* 9, 1888.

THE patient was a widow, æt. 65, who came under my care at St. Thomas's Hospital on December 1, 1887.

There was nothing of importance to note in the family history. With the exception of an attack of shingles nine years previously, and an attack of facial erysipelas six years later, she had been healthy until the onset of the present illness.

She stated that about seven months before she came under my notice her mouth gradually began to get dry, and that the dryness had steadily increased. To relieve the discomfort caused by the want of natural moisture she had to be constantly sipping fluid. She complained, too, that the act of swallowing was difficult and often painful. There was no history of the prolonged use of belladonna.

Figure1. Dr Hadden's case of dry mouth