Henrik Sjögren was born on the 13th of July 1899. One hundred years later the syndrome which bears his name is one of the most interesting and most intensively studied models of the systemic autoimmune rheumatic diseases. On the occasion of the centennial of Dr. Sjögren’s birth, and the convening of the VII International Symposium on Sjögren’s Syndrome in Venice, Italy, Clinical and Experimental Rheumatology wishes to celebrate his important discovery by dedicating to Henrik Sjögren one of its Classics in Rheumatology.

A humble gentleman at 100

F.A. Wollheim

The small town of Köping, west of Stockholm, at Lake Mälaren has reason to be proud of its scientific heritage, which also is of special interest to rheumatology. It was in this town’s only pharmacy that the autodidact and dispensing chemist Carl Wilhelm Scheele in the year 1776 (1) discovered uric acid when analysing urinary stones. This great scientist died prematurely at the age of 44 from a severe joint disease, perhaps gout. Scheele shares at least one experience with Henrik Sjögren, in that his first thesis was not much appreciated. However, just as in the case of Henrik Sjögren, thanks to perseverance, well deserved fame came with time.

How it started

Henrik Sjögren was born in Köping on the 23rd of July 1899 as the second of three children to a well-to-do merchant, and spent a happy youth with his elder brother and younger sister in the increasingly industrialised and growing town. After matriculation in 1918 (11) he attended medical school at the Karolinska Institutet and met his lifelong companion, Maria Hellgren. The romance inspired Henrik Sjögren to compose a waltz (see below), and the couple was soon married in Paris. Sjögren’s father-in-law was a prominent ophthalmologist at Karolinska, Ulrik Hellgren, who insisted that his son-in-law should enter upon an academic career. Henrik Sjögren, however, was more interested in the practice of medicine. Then one day in 1930 he encountered a woman patient suffering from dry and painful eyes, a moment which changed his life. He started to look for similar cases and later that year presented 5 cases of what he termed Keratoconjunctivitis sicca at a meeting in Stockholm (2).

Sjögren had spent some time in training at the institute of pathology at Karolinska. With this background he realised the need to use the microscope in order to characterise abnormal tissue. In 1933 he had diagnosed 19 patients and obtained conjunctival tissue from all of them. One patient had died and been submitted to an extensive post mortem examination. This material was presented as a doctoral thesis in 1933, written in German as then was common in Sweden (3). The family was pleased, but the defence turned out to be a less than pleasant affair. Sjögren’s former chief, the famous professor of pathology, Folke Henschen, gave the young doctor a hard time, and the committee decided that the work did not qualify Sjögren to attain the status of “Docent”, which then was a prerequisite for appointment to a staff position at one of the teaching hospitals.

Three decades in Jönköping

In 1935 the Sjögrens left Stockholm and moved to the match-producing centre of Jönköping, where Henry Sjögren remained as chief of ophthalmology for the rest of his professional life. There he published a number of scientific papers in which he extended and further consolidated the fundamental work already presented in his thesis. This was unusual at that time, when medical research in Sweden was strictly concentrated to the three medical schools in Uppsala, Lund and Stockholm.
In the late 1930s several papers were published in international journals using the term Sjögren’s syndrome, whereas another Swedish ophthalmologist, Stig Holm, in his 1949 paper (4) did not even cite Sjögren! While Holm soon vanished from the Sjögren’s literature, Henrik Sjögren continued to contribute scholarly papers long after his retirement in 1965 (56). A paper from 1951 published in Acta Ophthalmologica Scandinavica, however, serves well to illustrate his eminent and lasting contributions to the field (7). This paper is reproduced in its entirety here. In 1957 Dr. Sjögren was awarded the title of Docent by the then rather young medical school in Gothenburg, and in 1965 the Swedish government honoured him with the title of professor.

A major turning point in this uphill path to recognition was the translation of Henrik Sjögren’s German thesis into English in 1943 by the Australian ophthalmologist Bruce J Hamilton (8). In 1951 Sjögren was made an honorary member of the ophthalmologic societies in Australia and New Zealand. Henrik Sjögren has given a delightful account of his trip to “The antipodes” (9) (in Swedish). Dr. Sjögren travelled via Cairo, Karachi, Calcutta and Sydney to the congress in Hobart. Here he was met by Dr. Hamilton and all the local dignitaries. A limousine and chauffeur was placed at his personal disposal. From there the trip continued to New Zealand for more celebrations. The tour continued to Hawaii, San Francisco and finally New York. The interest in Sjögren’s syndrome was by now worldwide, but the travel report also shows Dr. Sjögren’s wide range of interests in other ophthalmologic problems, not the least corneal transplantation, a field to which he contributed significantly during his years in Jönköping.

Retirement in Lund
During the last 20 years of his life Henrik Sjögren lived in Lund. His continued interest in scientific developments was demonstrated by his active participation in European and other international ophthalmologic meetings. A year before his death he most fittingly served as one of the two honorary presidents at the First International Seminar on Sjögren’s Syndrome, organised by Dr. Rolf Manthorpe and Dr. Jan Ulrich Frause outside Copenhagen in 1986 (10). The other honorary president was Professor Jan G. Waldenström. At the opening ceremony (10) the delegates all enjoyed listening to the waltz mentioned above, dedicated to Dr. Maria Hellgren-Sjögren when the couple became engaged.

The fact that he now was a famous man never went to Dr. Sjögren’s head, however. When interviewed before the Copenhagen seminar, he was particularly amused to learn about the new Sjögren’s model in mice. He died the following year after suffering a stroke.

Henrik Sjögren’s legacy
Patients suffering from Sjögren’s syndrome had been described before 1930 (11), a fact that was fully acknowledged by Dr. Sjögren himself (3). Case reports and even small series of patients with glandular and extraglandular involvement had been published by various authors. Yet nobody challenges the designation of Sjögren’s syndrome. The first comment to be made is that Dr. Sjögren himself did not push for this at all. Indeed he simply suggested that the condition should be called Keratoconjunctivitis sicca rather than Keratitis filamentosa or any of the other earlier designations (11). Dr. Sjögren merely documented his continued interest and appreciation of the importance of the condition by publishing some 15 additional papers.

The problem of precise diagnosis occupied, and continues to occupy, considerable attention. In his thesis Dr. Sjögren devised the technique of staining with 1% rose bengal which is still in use. He also pointed out the importance of damaged cells for a positive staining, the usefulness of microscopic examination, and the interference caused by local anaesthetics in some patients. Furthermore, he stressed the risk of relying on the Schirmer’s test, which may show apparent low tear production in spite of normal lachrymal gland histology and function. This test also is affected by age and by some drugs. His critical views have been fully borne out in subsequent work published into the 1990s.
In the hypothalamus-pituitary-adrenocortical and gonadal axis in RA, M. Cutolo

**EDITORIAL**

Hypothalamus-pituitary-adrenocortical and -gonadal axis in RA / M. Cutolo

Classics in rheumatology / F.A. Wollheim

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**Hypothalamus-pituitary-adrenocortical and -gonadal axis in RA**

M. Cutolo

In the hypothalamus-pituitary-adrenocortical and gonadal axis in RA, certain changes have been observed. These changes may be related to the disease process itself or may be secondary to treatment with corticosteroids. The hypothalamus-pituitary-adrenocortical axis is involved in the regulation of the adrenal cortex, and alterations in this axis may affect the production of adrenal hormones. The hypothalamus-pituitary-gonadal axis is involved in the regulation of gonadal hormones and may be affected in RA.

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**34**

**Suggested reading in hypothyroidism**

J.W. Tindall

In hypothyroidism, certain changes have been observed in the hypothalamus-pituitary-adrenocortical and gonadal axes. These changes may be related to the disease process itself or may be secondary to treatment with corticosteroids. The hypothalamus-pituitary-adrenocortical axis is involved in the regulation of the adrenal cortex, and alterations in this axis may affect the production of adrenal hormones. The hypothalamus-pituitary-gonadal axis is involved in the regulation of gonadal hormones and may be affected in hypothyroidism.

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**40**

**Diabetes mellitus**

K. Stiller

In diabetes mellitus, certain changes have been observed in the hypothalamus-pituitary-adrenocortical and gonadal axes. These changes may be related to the disease process itself or may be secondary to treatment with corticosteroids. The hypothalamus-pituitary-adrenocortical axis is involved in the regulation of the adrenal cortex, and alterations in this axis may affect the production of adrenal hormones. The hypothalamus-pituitary-gonadal axis is involved in the regulation of gonadal hormones and may be affected in diabetes mellitus.

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**46**

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**52**

**Diabetes mellitus**

K. Stiller

In diabetes mellitus, certain changes have been observed in the hypothalamus-pituitary-adrenocortical and gonadal axes. These changes may be related to the disease process itself or may be secondary to treatment with corticosteroids. The hypothalamus-pituitary-adrenocortical axis is involved in the regulation of the adrenal cortex, and alterations in this axis may affect the production of adrenal hormones. The hypothalamus-pituitary-gonadal axis is involved in the regulation of gonadal hormones and may be affected in diabetes mellitus.
Henry Sjögren fully appreciated the importance of the age factor in this condition; most of the 80 patients whom he followed were over 50 years old. He also made the interesting observation that a girl with congenital alacrimia at the age of 5 years still had intact conjunctivae and no sicca complaints. This showed that a component of inflammation which we call autoimmunity was essential for the development of Sjögren's syndrome. Dr. Sjögren was furthermore impressed by the absence of septic complications, notably staphylococcal conjunctivitis, in sicca patients. Being an experienced microscopist, he noted that lymphocyte infiltration was a characteristic feature of the lesions, but also stressed their absence in very early lesions. This interesting observation still requires confirmation. It would be important to exclude the presence of pathogenic lymphocytes using modern staining methods in similar cases. Thus, analysis of infiltrating lymphocytes remains a fruitful field for further investigation, and may help to clarify the nature of the autoimmunity in Sjögren’s syndrome.

Much interest has been focused on the presence or absence of arthritis in Sjögren’s syndrome. Dr. Sjögren published a paper specifically on this topic (12), and also discussed it in several others. Based on the detailed experience which he had accumulated over the years in his care of at least 80 patients, he realised that half his patients also had rheumatoid arthritis, with a higher prevalence in the older age group and a lower prevalence in the mild cases. But Dr. Sjögren also wisely avoided any statements suggesting a causal relationship. He rather favoured the hypothesis of a common etiologic, perhaps infectious agent. What he did not realise was the clinical and immunologic difference between primary and secondary Sjögren’s syndrome, which was understood only much later (13). But he did notice the wide variability and the occurrence of incomplete and more general forms of the syndrome.

The endocrine system was high on the list of pathogenetic possibilities, and Dr. Sjögren commented on this in light of the recent discovery of Dr. Phil Hench. One intriguing observation of his in a number of papers was that his patients looked older than their stated age, and he ascribed this to a possible endocrine dysfunction. This would also be supported by the female preponderance of the syndrome. Dr. Sjögren realised that an elevated ESR and reduced secretion were often found in association in Sjögren’s patients. He also distinguished between Heerfordt’s febris uveoparotitide, Schulman’s disease and Mikulicz’s disease, the latter being characterised by glandular swelling with preserved secretory function in contrast to Keratoconjunctivitis, where secretory function is impaired or destroyed but swelling is not prominent. He strongly refuted the hypothesis of neurolysis in the pathogenesis of the sicca syndrome - a popular thesis among some investigators - based on its inherent anatomical improbability and on his own microscopic observations. Like so many later Sjögren’s investigators, Dr. Sjögren was not impressed by the therapeutic options available. One method that was being attempted in those days was the obliteration of the lachrymal canal, and his laconic comment was: “However, the result is by no means good in all cases”. Did it ever help?

Conclusion

One does not find in any of Dr. Sjögren’s papers a randomised, controlled study approach. Nevertheless, it is impressive how much solid knowledge Dr. Sjögren amassed with the simple use of clinical skills and a microscope. He listened to his patients, examined them carefully, and persisted in looking after them in spite of the meagre therapeutic options at his disposition. I am convinced that he was a very kind doctor to his patients, and took good care of the psychological aspects of their chronic condition as well. And I doubt that he ever fully realised the enormous impact on medical research which followed from his interest in Keratoconjunctivitis sicca.

Acknowledgement

Figure 1 was kindly provided by Mrs. Gunvor Rönn, the daughter of Henrik Sjögren, now living outside Stockholm. Mrs. Rönn has read this paper and informed me that, due to an illness in the family, Mrs Sjögren, much to her regret, could not accompany her husband on the world tour in 1951 as had been originally planned.

References