Animal model for Sjögren’s syndrome
—Experimental autoallergic sialadenitis in SL/Ni mice—

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Sjögren’s syndrome is an autoimmune disease in which there is a progressive loss of salivary and lacrimal gland function because of direct attack by infiltrating lymphoid cells. Although the exact mechanism by which the glands are destroyed is unknown, numerous immunological studies suggest both T- and B-lymphocytes are involved. At times, Sjögren’s syndrome and other autoimmune diseases may coexist with high frequency in the same patient. Experimental autoallergic diseases have been produced in various organs in order to develop animal models of immunologically mediated diseases in man. Recently, an experimental autoallergic sialadenitis with various grades of lesion and rapid time of onset has been reported by White et al.1-4) in rat. But attempts to obtain an animal model resembling Sjögren’s syndrome in man have been unsuccessful. On the other hand, NZB/NZW mice, which are generally considered models for human systemic lupus erythematosus, spontaneously develop generalized lymphoid cell infiltration, especially in the salivary glands. It has been thought that pathological changes of the salivary glands occurring in NZB/NZW mice are similar in most respects to those which characterize Sjögren’s syndrome in man5,6). We have also attempted to obtain a laboratory model for Sjögren’s syndrome overlapping other autoimmune diseases and have examined the salivary glands in SL/Ni mice which spontaneously develop PN-like arteritis, SLE-like glomerulonephritis and occasional malignant lymphoma. As a result of our previous histopathological examination of SL/Ni mice, it is thought that SL/Ni mice is a good model for human overlap-syndrome in the early stage of Sjögren’s syndrome7.8). The purpose of the present study is to produce more severe salivary gland lesions in SL/Ni mice.

Material and Method

The animals, 10 month old female SL/Ni mice, were divided into several groups. The mice examined were sixty in total. Submandibular gland tissue was obtained from the same strain mature mice, the tissue was excised, cleaned of fascia and homogenized in an equal volume of phosphate-buffered saline. The homogenate was then emulsified in an equal volume of Freund’s complete adjuvant (DIFCO). The antigenic emulsion was injected subcutaneously into the four foot pads of mice, followed by intravenous injection of absorbed diphtheria-pertussis-tetanus combined vaccine (Takeda Chemical Industries, Ltd.). Control mice were nontreated or injected with saline emulsified with the same adjuvants. Thirty animals were sacrificed at 1, 2 and 4 weeks after the first immunization. In the other thirty animals, second immunization was performed in the same manner at 2 weeks after first immunization and animals were sacrificed at 1, 2 and 4 weeks after the second immunization. Complete autopsies were per-
formed on all animals, and the submandibular, sublingual and parotid glands were examined histopathologically.

Result

Slight to moderate lymphoid cell infiltrations were present in about 80 per cent of the control mice. On the other hand, moderate to severe lymphoid cell infiltrations were found in almost all of the experimental mice (Figs. 1 and 2). It was clear that the salivary gland lesions were more extensive in the experimental mice than in the controls. Furthermore, lymphoid cell aggregates were more widespread and more dense, and parenchymal destruction was more marked in the experimental groups. Complete alteration of whole glandular tissue with fibrosis and diffuse lymphoid cell infiltration was found in some cases (Fig. 3). In the foci of lymphoid cell aggregation, thickened duct wall suggesting epithelial proliferation was found (Fig. 4). These salivary gland changes were most prominent in the submandibular glands, less in the sublingual glands and still less in the parotid glands. Although there was a tendency for the severest salivary gland lesions to be frequent in the group which was sacrificed at two weeks after the second immunization, no statistical difference in severity was noted in each group.

Photomicrographs of sialadenitis in the submandibular glands of SL/Ni mice. Figures 1 and 2 showed marked accumulations of infiltrating lymphoid cells (original magnification: $\times 100$). Figure 3 showed alteration of whole glandular tissue with fibrosis and diffuse lymphoid cell infiltration (original magnification: $\times 100$). Figure 4 showed thickened duct wall in the aggregation of lymphoid cells (original magnification: $\times 400$).
Discussion

There have so far been several reports on systemic histopathological observations in experimental autoallergic sialadenitis. However, these experiments are merely "sialadenitis" and should not be regarded as laboratory models for Sjögren's syndrome in the strict sense, since Sjögren's syndrome in man is a disease which shows both organ-specific and non-organ-specific characteristics. It has been recognized that NZB/NZW mice develop spontaneously many of the features seen in Sjögren's syndrome associated with autoimmune disorders\(^5,6\) but the severity of histopathological changes of the salivary glands are conflicting. We have attempted to obtain a new animal model for Sjögren's syndrome and examined the salivary glands in SL/Ni mice\(^7,8\) since Sjögren's syndrome has a relationship to other autoimmune diseases and shows various immunological disorders. SL/Ni is an inbred strain of albino mouse established in Japan. It was originally known as a strain with a high incidence of MuLV-induced B-cell lymphoma. Since 1970, however, after some genetic alterations in the H-2 and adjacent lesion, the incidence of lymphoma began to decrease and immune complex glomerulonephritis very similar to that in SLE, fibrinoid arteritis much like that of PS and various immunological disorders appeared spontaneously with considerably high incidence. It is thought that the immune complex formed against various virus-components well play a role of the pathogenesis in SL/Ni mice. In a previous histopathological study it was reported that the salivary glands of female SL/Ni mice showed lymphoid cell infiltration in various degrees arising in the second month and progressing in incidence and severity with aging\(^7,8\). Although there were no severe lymphoid cell infiltration with formation of epi-myoepithelial islands as seen in the typical Sjögren's syndrome in man, the findings suggested that SL/Ni mice might be a good model for the human overlap-syndrome in the early stage of Sjögren's syndrome.

The result of the present study to produce more severe salivary gland lesions in SL/Ni mice showed marked lymphoid cell infiltration with proliferation of duct epithelial cells in part, and complete alteration of whole salivary gland tissue in some cases. These findings were similar in most respects to those which characterize Sjögren's syndrome in man. The details will be reported further following electron microscopic and immunohistochemical examinations.

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References