(2) Genetic and Some Environmental Factors Concerning with Development of Autoimmune Diseases, with Special Reference to Autoimmune Hepatitis

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From the family studies of 6 patients with autoimmune hepatitis (active chronic hepatitis, lupoid type), it has been demonstrated that serological abnormalities in immunoglobulin levels and incidence of humoral auto-antibodies such as anti-liver, anti-smooth muscle, anti-thyroid and anti-nuclear antibodies were frequently encountered in the family members of these patients. Occurrence of ANF and thyroid antibody seemed to be preferable in the female members (Table 1). Among the relatives of the patients with autoimmune hepatitis, an increased incidence of other autoimmune diseases, e.g. chronic thyroiditis, RA and Behçet's disease, as well as chronic hepatitis with abnormal immunological features has been observed.

Table 1. Family Studies on Autoimmune Hepatitis —Serological—

Number of propositus	Number of Relatives	Serological Abnormalities							
		Hyper γ -glob	IgG	IgA	IgM	Anti- liver	Anti- smooth muscle	ANF	Anti- thyroid
6	14 males	6/12	6/13	1/13	4/13	8/13	2/13	1/13	4/13
	18 females	9/18	6/15	2/15	8/15	7/15	3/17	5/18	9/18

Fig. 1 shows a representative family, in which not only abnormal levels of IgG, IgA and IgM but also various circulating autoantibodies are found among the members thru 3 generations.

No abnormalities in cellular immunity were encountered in 4 relatives, as evaluated by macrophage migration inhibitory factor to liver homogenate and DNA. From above, it could be concluded that genetic predisposition to autoimmune reactions seemed to be inherited in autosomal dominant fashion. From the family studies on 13 patients with SLE, similar findings in serological abnormalities and modes of inheritance observed in autoimmune hepatitis have been obtained even in SLE (Table 2).

The above abnormal immunological events would be controlled genetically and also based on the deranged immunological surveillance.

We reported previously 12 cases of autoimmune hepatitis associated with chronic thyroiditis and found abnormal immunological predisposition observed in some families of the patients. Reuber and Glover reported that chronic thyroiditis probably due to immune mechanism and liver cirrhosis developed in Buffalo strain rats by the administration of CCl_4 . In our animal experiments, we have not observed chronic thyroiditis at all in control rats including Wistar, Sprague-Dowrey and Donryu strain rats, although the incidence of chronic thyroiditis in Buffalo strain rats was frequent. These experimental findings indicate that genetic factor would be one of very important factors concerning with development of the autoimmune disease.

Since Australia antigenemia and cellular antibody to the antigen were not detected in a majority of the patients with autoimmune hepatitis, Australia antigen itself seems to be little related to persistence of autoimmune mechanism.

	Immunoglobulin (mg/dl)			Antibodies				Australia Antigen
	IgG	IgA	IgM	Liver	SMA	Thyroid	ANF	
D74F	3,340	586	750	(+)	(-)	(±)	(-)	(-)
→ P48F	1,932	177	154	(+)	(+)	(-)	(+)	(-)
A42M	2,252	336	148	(-)	(±)	(±)	(-)	(-)
B37M	1,636	48	408	(-)	(±)	(±)	(-)	(-)
C33F	1,440	322	280	(-)	(-)	(-)	(-)	(-)
E28F	1,328	208	128	(-)	(-)	(-)	(-)	(-)
F22F	1,060	212	202	(-)	(-)	(+)	(-)	(-)
G14M	1,544	176	108	(+)	(-)	(-)	(-)	(-)
H17F	2,512	336	218	(-)	(±)	(±)	(-)	(-)
I13F	1,456	70	408	(-)	(-)	(+)	(-)	(-)
J10F	1,288	48	468	(+)	(-)	(+)	(-)	(-)

Fig. 1. Pedigree of Family K.

Table 2. Family Studies on SLE —Serological—

No. of Propositus	No. of Relatives	Serological Abnormalities							
		Hyper- γ -Gt	Ig G	Ig A	Ig M	ANF	RAT	Anti-TG	Anti-MS
13	21 males	4/21	9/21	2/21	4/21	1/21	1/21	1/21	5/21
	27 females	9/27	7/27	10/27	12/27	4/27	2/27	6/27	12/27