

Autoimmune Pathogenesis in Thyroid Diseases

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= Abstract = Many evidences have been presented that autoimmunity plays a major part in the pathogenesis of thyroid diseases. Autoimmunity in thyroid diseases shows up as clinical and laboratory findings of disordered humoral and cellular immunity and immunogenetic background of the patients. So, to make clear the significance of humoral immunity in the autoimmune pathogenesis of thyroid diseases, most of the autoantibodies found in autoimmune thyroid diseases are discussed about their characteristics and implications. Especially in Graves' disease patients, TSH receptor antibodies are now considered to play a causative role in the genesis of disease. Our data about every aspect of these antibodies are presented. In the patients with primary myxedema TSH receptor antibodies are suspected to behave themselves as a blocker of TSH action. Then the author presents our findings about blocking TSH receptor antibodies. Cellular immunity influences the immune tolerance to self antigens in the patients with autoimmune thyroid diseases. The author reviews the roles of cellular immunity in the autoimmune thyroid diseases in the aspects of the disordered functions of the cellular immunity and its further regulatory roles in the humoral immunity, presenting our data about the functional aberrations of the regulatory immunocytes and thyrocytes. Genetic and immunogenetic background of the patients with autoimmune thyroid diseases are then reviewed with the data on HLA and disease association in Koreans, analyzing their significance in the pathogenesis of autoimmune thyroid diseases. The author suggests the possible mechanisms in the autoimmune pathogenesis in thyroid diseases with the present findings.

Key words: *Autoimmunity, Pathogenesis, Graves' disease, Primary myxedema, Hashimoto's thyroiditis*

INTRODUCTION

Autoimmune mechanism has been proposed to be involved in the pathogenesis of thyroid diseases since Doniach and Roitt (1956) proved precipitating antithyroglobulin antibodies against the human thyroglobulins in the sera of the patients with Hashimoto's thyroiditis and Witebsky and Rose (1956) developed experimental thyroiditis in rabbits by immunization with thyroid antigens (Cho 1985d). Graves' disease, Hashimoto's thyroiditis, primary myxedema and endocrine exophthalmopathy have been thought to be the 'autoimmune thyroid diseases' which are caused by autoimmune

mechanism.

These thyroid diseases appear to be caused by the common pathogenetic mechanisms and are even considered to be 'one' syndrome which shows diverse spectra of clinical features considering two or more disease entities are found concurrently in one patient and a patient is often found to be afflicted with one disease after he had contracted another autoimmune thyroid diseases.

Recent advances in the knowledge and experimental technology in the field of immunology have elucidated many aspects of the autoimmune mechanisms in thyroid diseases. Especially there have been so many reports and studies about autoimmune thyroid diseases that the thyroid diseases such as Graves' disease and Hashimoto's thyroidi-

tis are considered to be good models of the autoimmune diseases and that the pathophysiologic features of the autoimmune thyroid diseases have become the foci of interests in the fields of immunology and genetics. In this review, the author will cover various viewpoints about autoimmune aspects of the thyroid diseases and describe our observations regarding the autoimmune thyroid diseases during recent several years and present the future prospects of the autoimmunity in this field of thyroidology.

Evidences of Autoimmunity in the Pathogenesis of the Thyroid Diseases

There have been many reports from various standpoints which assert that autoimmune mechanisms are the major causes of certain thyroid diseases such as Graves' disease and Hashimoto's thyroiditis.

In histopathologic aspects, thymic hyperplasia was observed in both diseases and lymphocyte infiltration and immunoglobulin deposition were found in the thyroid glands of both diseases (Ahn *et al.* 1985).

Clinical observations showed frequent lymph node hyperplasia and splenomegaly, increased number of lymphocytes in peripheral blood, and increased concentration of immunoglobulins and circulating immune complexes in both diseases. Both are frequently associated with other diseases which have been considered to be of autoimmune origin. Myasthenia gravis, Addison's disease, idiopathic thrombocytopenic purpura, pernicious anemia and insulin dependent diabetes mellitus have been reported to be associated with Graves' disease. Hashimoto's thyroiditis is also reportedly accompanied by Sjogren's syndrome, chronic lupoid hepatitis, Addison's disease and myasthenia gravis.

From the viewpoints of serology, thyroid autoantibodies were found in the sera of the most patients with autoimmune thyroid diseases and there have been many experimental reports that cellular immune mechanisms were also involved in the pathogenesis of the autoimmune thyroid diseases.

In the aspect of genetics, the relatives of patients showed the increased prevalence of autoimmune thyroid diseases and they were also found to have autoantibodies against the thyroid antigens in about 50% of the time. The association of HLA phenotypes and Graves' disease has long been thought to be further evidence of immunogenetic mechanism in the genesis of the thyroid diseases (Cho *et al.*

1987c).

Humoral Immunity

Antithyroglobulin antibody

Thyroglobulin is measured in the sera of normal persons with concentration of 0 to 50 pmole/L and is increased in concentration when the thyrocytes are stimulated or when the thyroid tissues are damaged. Thyroglobulin whose molecular weight is 670,000 is reported to have about 40 epitopes, but there are only six epitopes at most in human thyroglobulin which are recognized by antithyroglobulin antibodies (Nye *et al.* 1980).

Antithyroglobulin antibodies are usually polyclonal in nature. Most of the antibody activity is found in the IgG class, up to 20% being found in IgA and never more than 1% in IgM. 68% of IgG are IgG1, 19% are IgG2, 7% are IgG3 and 6% are IgG4, and thus more than 70% of these antibodies can fix complements in principle. But these immunoglobulins were not found to fix complements *in vivo* (Hay *et al.* 1973). This phenomenon may be accounted for by the fact that the antigenic epitopes within thyroglobulin for the autologous antithyroglobulin antibodies are too few and sparse to activate the complement system well. The above features make it unlikely that the activity of antithyroglobulin antibody would determine the degree of tissue damage in autoimmune thyroid diseases.

Current assay methods for antithyroglobulin antibodies comprise conventional tanned hemagglutination method, recently developed radioimmunoassay and enzyme linked immunosorbent assay. According to our observations, the prevalence of antithyroglobulin antibodies in normal Koreans was 1.9% in men and 5.0% in women with tanned hemagglutination method (Lee *et al.* 1986). The analysis of age-specific prevalence in normal population gave the maximal values around forty and fifty. The group whose antibody titer was elevated had low T3 values and high TSH values but normal T4 values. This group was suspected to be the population having subclinical autoimmune thyroiditis.

Regarding the detectable level of autoantibodies with radioimmunoassay as being positive, normal Korean men had the antithyroglobulin antibodies in 54.4% and normal women had antibodies in 36.8%. No difference was found in age-specific prevalence of antibodies (Chung *et al.* 1987). The difference in the prevalences of thyroid autoantibodies measured by two methods can be accounted for by inclusion of persons with low titer antibodies

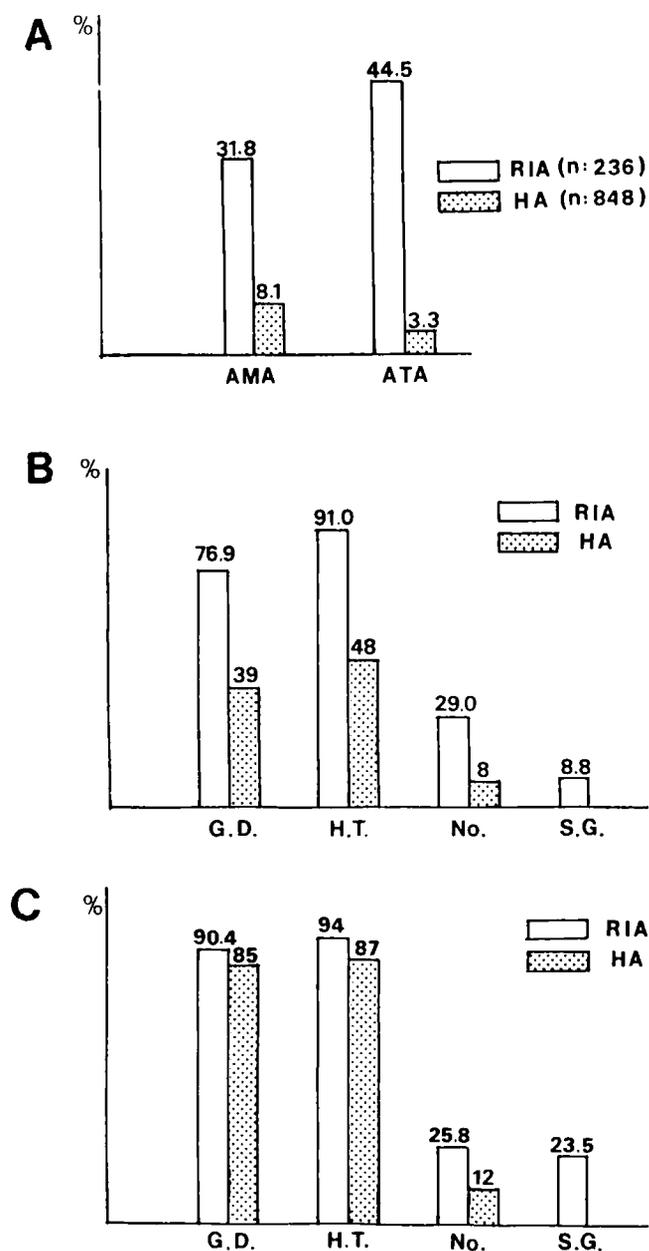


Fig. 1. Prevalence of antimicrobial antibody and antithyroglobulin antibody in normal controls (A). Prevalence of antithyroglobulin antibody (B) and antimicrobial antibody (C) in the patients with thyroid diseases by radioimmunoassay (RIA) and hemagglutination test (HA). (G.D.; Graves' disease, H.T.; Hashimoto's thyroiditis, No.; nodule, S.G.; Simple goiter. Modified from Chung JH *et al.* Kor. J. Nuc. Med. 1987, 21:136-137)

by radioimmunoassay in the evaluation of prevalence in normal.

Forty eight % of Graves' disease patients and thirty nine % of Hashimoto's thyroiditis patients had antithyroglobulin antibodies with hemagglutination method. Ninety one % of Hashimoto's thyroiditis patients and seventy seven % of Graves' disease

patients showed positive tests with radioimmunoassay for antithyroglobulin antibodies (Fig. 1).

Some of the patients with thyroid adenoma and a few patients with nodular goiter had high titer antibodies with radioimmunoassay. The implication of these findings in the aspects of autoimmunity is yet to be solved. Because normal persons also have low titer autoantibodies, with more sensitive assay method of radioimmunoassay, we set the cutoff value of 9 U/ml as an upper limit for normal persons, after analyzing the distribution of the antibody titers in normal and patient groups. With this value as a standard the positive ratio of antithyroglobulin antibodies in normal population was shown to be 18.6% (Chung *et al.* 1987).

Antimicrobial antibody

Thyroid microsomal antigens have been reported to be parts of smooth endoplasmic reticulum and to comprise lipoproteins of the membranes of exocytic vesicles which contain newly made thyroglobulins. Recent reports insist that the enzymes of thyroid peroxidase which take part in the biosynthesis of thyroid hormones are the microsomal antigens of the thyroid (Mariotti *et al.* 1987).

The activity of antimicrobial antibodies is predominantly associated with IgG1. The microsomal antigen is strictly organ-specific and species cross reactivity is restricted to primates. It has been known that antimicrobial antibodies have the capability to activate complements and exert cytotoxic effects on the cultured thyrocytes. In contrast to antithyroglobulin antibodies, antimicrobial antibodies were found to have an interrelation with the degree of histopathologic changes of thyroid tissue in Hashimoto's thyroiditis.

The assay methods are the same as those of antithyroglobulin antibodies. With tanned hemagglutination method we have found the prevalence of 4.4% in normal Korean men and 12.4% in Korean women, and the maximal prevalence around forty and fifty in age (Lee *et al.* 1986). With radioimmunoassay antimicrobial antibodies were detected in 42.7% of normal Korean men and in 23.2% of Korean women (Chung *et al.* 1987). The population with low titer antibodies especially in normal men contributed mostly to the increase in the prevalence of antithyroglobulin antibodies in normal men as in the case of antithyroglobulin antibody measurement. If we took 7.5 U/ml as a cutoff value for the upper limit of normal range through the analysis of the distribution of the autoanti-

bodies, the prevalence of antimicrosomal antibodies in apparently normal Koreans was 15.7%.

The patients with Hashimoto's thyroiditis had the antibodies in 87% and those with Graves' disease had the antibodies in 85% with hemagglutination method, and those with Hashimoto's thyroiditis were found to have these antibodies in 94% and those with Graves' disease in 90% with radioimmunoassay (Fig. 1).

The facts that we can find autoantibodies in many normal persons even if they were in low titer and that high titers of normally present autoantibodies are found in the patients with autoimmune thyroid diseases suggest that these are the points which are to be pursued about their pathophysiological significance in terms of idiotype-antiidiotype immune network in healthy subjects and the probable derangement of its balance in disease state.

Autoantibodies to colloid

In some patients with Hashimoto's thyroiditis or Graves' disease, some investigators found the immunofluorescence from the colloid of the sliced thyroid tissue treated with the sera of these patients. They reported that these immunofluorescence did not disappear after the adsorption of the sera with purified thyroglobulin (Mori *et al.* 1971). According to these experiments, the antibodies against colloid were supposed to be different from antithyroglobulin antibodies, but the pathological significance of these antibodies is still far from clear.

Anti-thyroid hormone antibody

Autoantibodies to thyroxine and triiodothyronine have been observed in a few of the patients with Hashimoto's thyroiditis. These antibodies showed cross reactivity against thyroglobulin. Some investigators manifested that these antibodies were found by and large in the patients with Graves' disease whose thyroglobulin levels in the sera were markedly elevated. These antibodies are usually discovered incidentally by their interference with the radioimmunoassay of thyroid hormones in that the antibodies in the patient's sera bring about falsely high or low values of thyroxine or triiodothyronine according to the separation methods.

Two cases of antithyroid hormone antibodies that we have experienced were also found incidentally. The same sera of the patients gave a falsely high value of T4 by solid phase radioimmunoassay and unmeasurably low value of T4 by polyethylene glycol separation method (Cho *et al.* 1986a). These

findings indicated that there was some substance(s) in the sera with the capacity of specific binding with thyroxine. We found that this substance was IgG against thyroxine after some steps of physicochemical characterization. One of these cases was primary myxedema and the other was chronic thyroiditis associated with systemic lupus erythematosus. Antithyroxine antibodies of chronic thyroiditis had the cross-reactivity with triiodothyronine (Fig. 2).

The significance of antithyroxine antibodies has not been well documented. Some of the anti-T3 antibodies reportedly played inhibitory role against the peripheral action of T3 hormone (Karlsson *et al.* 1977). There were suggestions that the action of anti-thyroid hormone antibodies were probably because of cross reactivities of antithyroglobulin antibodies with thyroid hormones considering they were frequently found in the patients with antithyroglobulin antibodies of high titer. The pathogenetic and clinical significance of these autoantibodies remains to be elucidated.

TSH receptor antibodies

1) Historical background

In 1956 Adams and Purves found some substance in the sera of patients with Graves' disease stimulating the thyroid gland of guinea pigs. This substance was slower in onset of action and longer in duration of action than thyroid stimulating hormone (TSH). They called it long acting thyroid stimulator(LATS). Since then, LATS has been found to comprise immunoglobulin G, to bind to thyrocytes, to have the binding activity at its F(ab)₂ portion, and to be the cause of Graves' disease as an autoantibody against thyroid membrane. But LATS were observed only in 20 to 60% of patients with Graves' disease and the activities of LATS were not correlated with the severity of hyperthyroidism. In consequence there arose much suspicion in its probable role in the pathogenesis of Graves' disease.

In 1967 Adams and his colleagues found another immunoglobulin G in the sera of the patients with LATS negative Graves' disease, which protect LATS from being adsorbed and consequently neutralized by human thyroid cellular membrane in LATS bioassay. They called this IgG LATS-protector (LATS-P). LATS-P did not stimulate the animal's thyroid gland but did have influences on the human thyroid membrane and so has been known as a human thyroid stimulator. LATS-P was found in

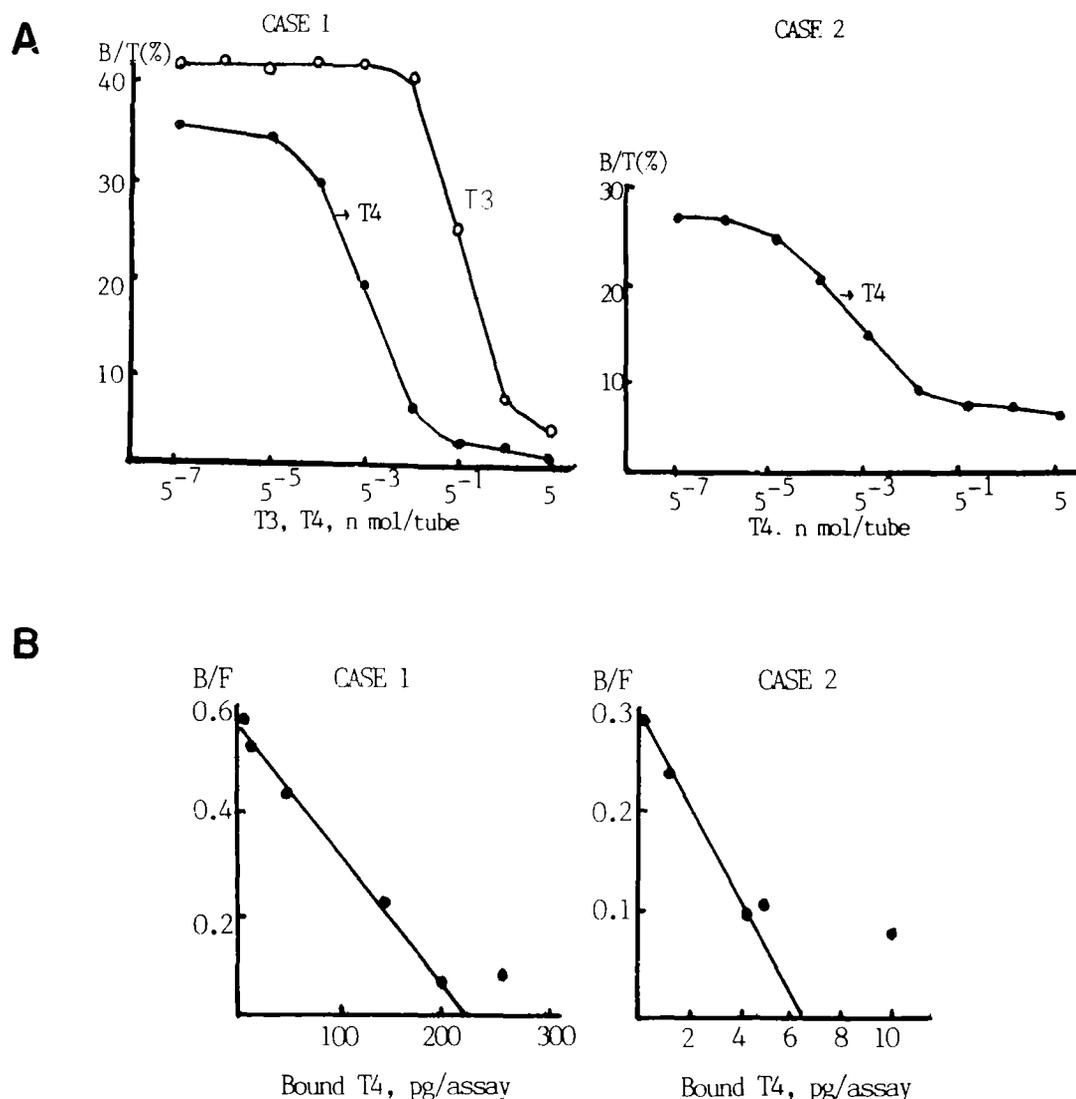


Fig. 2. Inhibition of ¹²⁵I-T₄ binding to patient's IgGs by cold T₃ and T₄ (A) in chronic thyroiditis associated with systemic lupus erythematosus (case 1) and in primary myxedema (case 2). Scatchard plots of T₄ binding to patient's IgGs (B). In case 1, K_a was 6.1×10^8 l/mol and binding capacity was 4.8 ng T₄/mg-IgG. In case 2, K_a was 9.2×10^9 l/mol and binding capacity was 0.11 ng/mg-IgG (Reprinted from Cho BY *et al.* Kor. J. Int. Med. 1986a, 1:11).

more than 90% of patients with Graves' disease and its activities are shown to be in good correlation with the thyroid function.

2) Principles of assay methods and nomenclature

Since 1970 many investigators developed various assay methods for measurement of thyroid stimulating antibodies and called these thyroid stimulating antibodies in so much different ways that the readers would have been very much confused. But, soon after the antigens of these antibodies were known to consist in TSH receptors of thyrocyte membranes, these antibodies came to be called as 'TSH receptor antibodies' (TRAb) *in toto*.

TRAb are assayed by two fundamentally different principles. The first one is to measure the activities of patient's sera to stimulate the thyroid; assessing the numbers of colloid droplets induced by adding the patient's sera into human, murine or porcine thyrocytes in culture or into sliced thyroid tissues, or measuring the concentration of cyclic AMP in the cultured thyrocytes stimulated with the patient's sera. The stimulating antibodies measured with these methods are called thyroid stimulating antibodies (thyroid stimulating immunoglobulins; TSI).

The second one is to measure the capacity of patient's sera to inhibit the binding of TSH to TSH

Table 1. The results of immunofluorescent findings in the thyroid glands of Graves' disease and Hashimoto's thyroiditis (Reprinted from Ahn I-M *et al.* Seoul J. Med. 1985, 26:151)

| Disease | No. | FBM | % | IFS | % | |
|-------------|-----|-----|-----|-----|----|-----|
| Graves' | 21 | 20 | 95 | 1 | 5 | |
| Hashimoto's | 11 | 5 | 45 | 7 | 63 | |
| FBM deposit | | | | | | |
| | No. | IgG | IgA | IgM | C3 | Fbg |
| Graves' | 21 | 20 | 2 | 1 | 15 | 6 |
| Hashimoto's | 11 | 5 | 0 | 0 | 3 | 3 |
| IFS deposit | | | | | | |
| | No. | IgG | IgA | IgM | C3 | Fbg |
| Graves' | 21 | 1 | 0 | 0 | 0 | 1 |
| Hashimoto's | 11 | 6 | 1 | 1 | 1 | 0 |

FBM: Follicular basement membrane

IFS: Interfollicular space

Fbg: Fibrinogen

receptors on the thyrocyte membranes; measuring the inhibitory activities of patient's sera on the binding of bovine TSH to the particulate or solubilized TSH receptors within the thyrocyte membrane. These are named TSH binding inhibitory immunoglobulins (TBII) for its inhibitory activity.

3) Characteristics of TSH receptor antibodies

TRAb are known to be composed of immunoglobulin G. Some reported that IgM and IgA were also deposited within thyroid glands and that IgM from the sera of patients with Graves' disease showed TSI or TBII activities. But there has been no agreement about the idea that other isotypes of immunoglobulins than IgG are related with the pathogenesis of Graves' disease. We also observed that among 21 patients with Graves' disease whose thyroid glands were studied with immunofluorescent staining for immunoglobulin isotypes the deposits of IgM or IgA were found in 3 cases at the basement membranes of thyroid follicles (Ahn *et al.* 1985). It is still not certain whether these are the cytotoxic antibodies associated with the accompanying thyroiditis or the TRAb stained *in situ*, or both (Table 1).

Binding activity of the TRAb reside in F(ab)₂ portion of IgG. The TRAb lose their binding capacity if long and short chains of these immunoglobulins are split and these activities are restored if reunion of both chains is carried out. It is not certain which subclasses of these IgG antibodies stimulate the thyroid function *in vivo*. TRAb are of

polyclonal origin and are now considered to comprise clones with heterogeneous biologic functions. The balance of the respective clones of TRAb would explain the changes of the composition of TRAb and the clinical features during treatment in patients with Graves' disease.

4) Antigens

Although TSH receptors are considered to be antigens for TRAb, it is still uncertain which part is the exact binding site of these receptor antibodies within thyrocyte membrane. The assay results of TRAb activities measured using solubilized thyroid membrane are similar to those measured using crude membrane extracts of thyroid tissue. Even if guinea pig fat cell membrane or testicular cell membrane which have only TSH receptor antigens are used as a source of TSH receptors in radioreceptor assay of TBII, no difference in assay results was reported in the measurement of TRAb activities. These findings made it very likely that TSH receptors themselves are the antigens for TRAb. TSH receptors are membrane-bound glycoproteins. About one thousand receptors are present on the surface membrane of one thyrocyte. The molecular weight of the whole receptor molecule is thought to be about 70,000 daltons and Smith and his colleagues (1986) reported that this receptor consisted of A subunit which bound to TSH molecule and B subunit which are immersed within the cellular membrane.

Kohn contended that TSH receptor consisted of gangliosides and glycoproteins, and he speculated

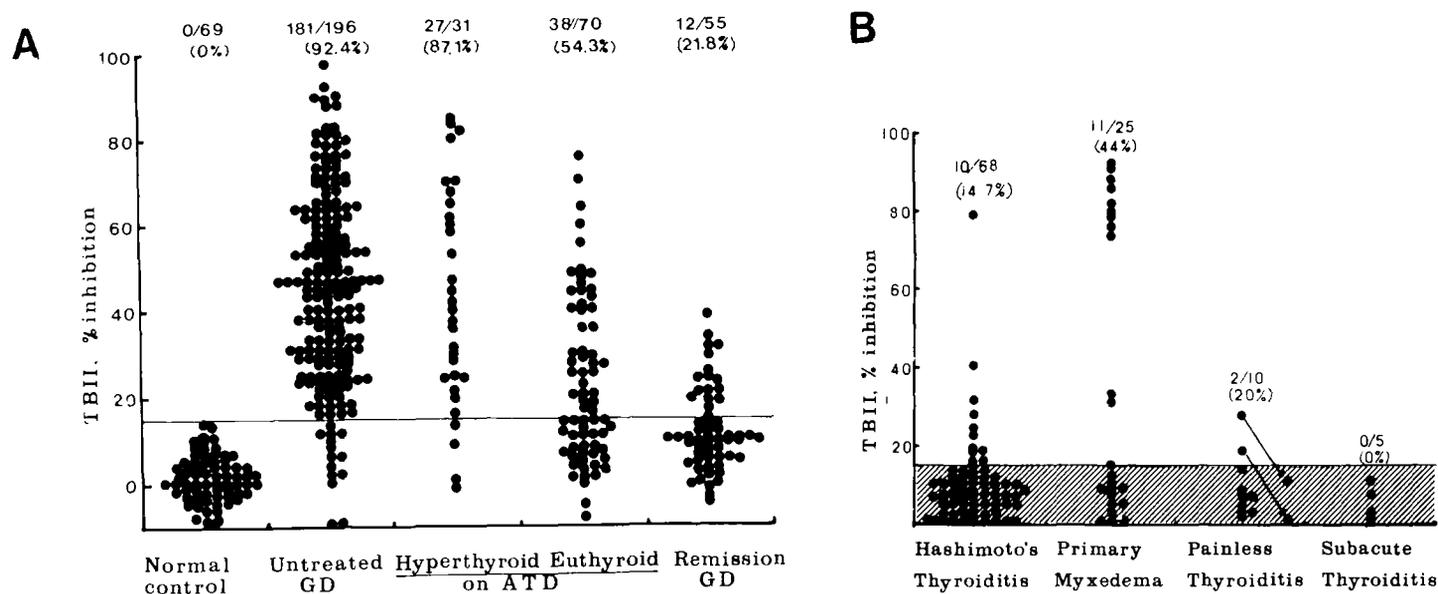


Fig. 3. TBII activities with radioreceptor assay in the sera from normal control subjects, Graves' disease patients with various stages of thyroid function (A), and the patients with other thyroid diseases (B). (TBII; TSH binding inhibitory immunoglobulin, GD; Graves' disease, ATD; antithyroid drugs. Modified from Koh C.-S. Kor. J. Nuc. Med. 1986, 20:89-90).

that the antibodies against ganglioside portion stimulated thyroid cells and those against glycoprotein parts blocked TSH binding to TSH receptors (Valente *et al.* 1982). These contentions are considered to be compatible with our previous interpretations that the clinical features of a patient in his disease course were the reflections of the changes of the balance of the autoantibody clones which had different biologic functions respectively (Cho 1987d).

It is to be clarified whether the binding sites for TRAb and those for TSH are the same or not, though the results of immunoprecipitation experiments and neutralization tests show that TSH and antibodies compete for the same site.

5) Prevalence in thyroid diseases

The prevalences of TRAb in autoimmune thyroid diseases show much discrepancy according to the assay methods. The prevalences of TBII activities in patients with Graves' disease is variable from 70 to 90% in the literature (Cho 1987d). We found that 83% and 92% of the patients with untreated Graves' disease had detectable TBII activities in two series (Cho *et al.* 1985a; Koh 1986, Fig. 3). With TSI assay methods, many investigators have reported that the prevalence of positive TSI activities in Graves' disease was about 90% (Cho 1987d). We also found that 92.5% of the patients

with Graves' disease had TSI activities using the assay system measuring the generated cyclic AMP in cultured rat thyroid cell lines; FRTL-5 cells (Shong *et al.* 1987b, Fig. 4).

TSI and TBII activities in the patients with Graves' disease showed significant correlation, albeit not so strong with r^2 value of 0.43 (Shong *et al.* 1987b). This observation and the finding that TSI activities were not observed in patients with primary myxedema despite the strong activities of TBII suggest the followings; TRAb are the set of clones which have the different functional effects onto the thyroid cells, and TRAb in patients with Graves' disease also include the blocking or binding-but-not-stimulating antibodies beside the stimulating antibodies against TSH receptors within the thyroid membrane. Of course, we should take into account the fact that the lower sensitivity of TBII assay method would have contributed to the not-so-close consistency between TSI and TBII activities.

We could not detect TRAb in the sera of some patients with Graves' disease (8% by TBII and 7.5% by TSI methods, Koh 1986; Shong *et al.* 1987b). It is uncertain whether this is because of the lower sensitivity of the assay methods or because the disease entity of Graves' disease include heterogeneous populations in its pathogenesis and

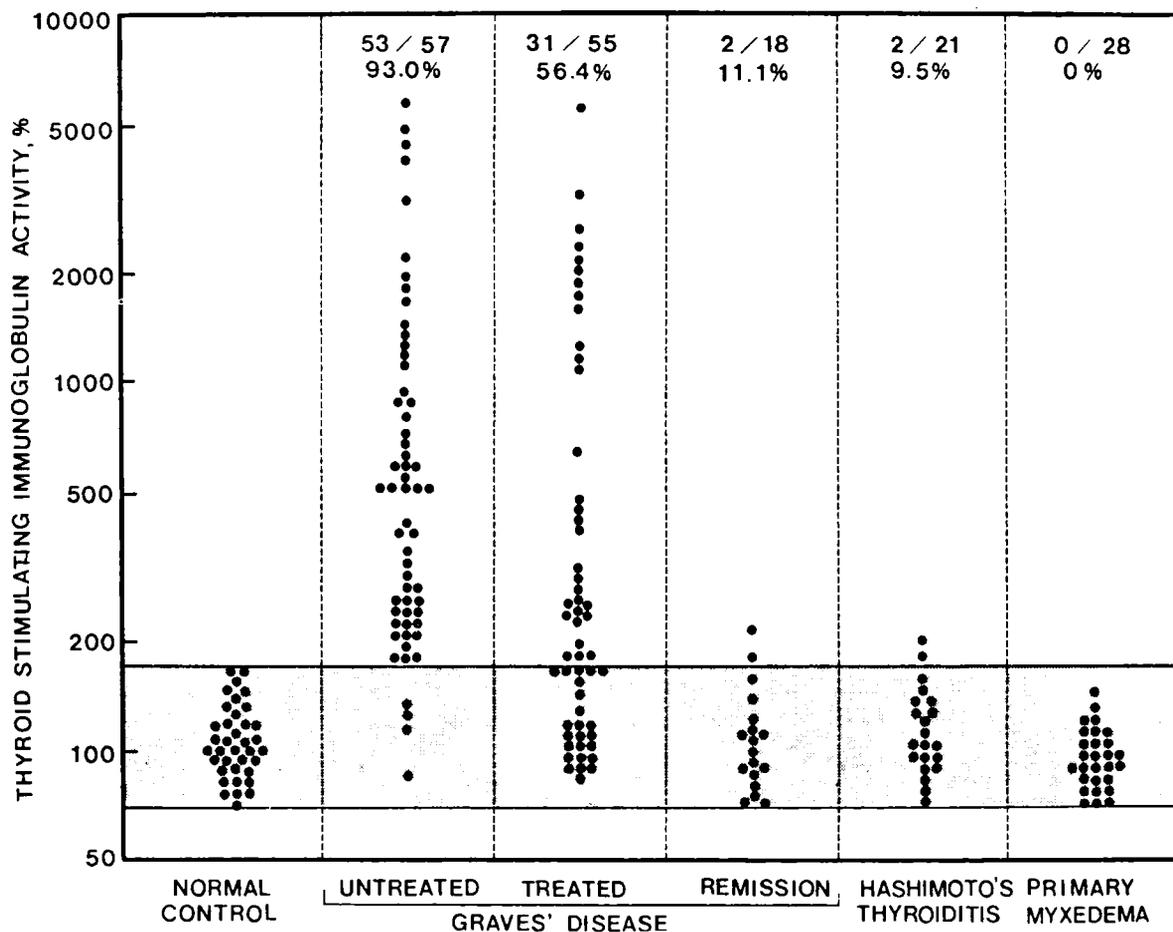


Fig. 4. TSI activities in normal controls, Graves' disease patients, the patients with Hashimoto's thyroiditis, and the patients with primary myxedema represented by cyclic AMP production rate in FRTL-5 cell system. (TSI; thyroid stimulating immunoglobulin. From Shong YK. *et al.* Kor. J. Int. Med. (Abstr. 39) 1987b, p185).

pathophysiology. Some authorities in Europe assumed that 'disseminated autonomy' of the thyroid gland would be the cause of hyperthyroidism in some of the patients with Graves' disease (Schleusener *et al.* 1980). This hypothesis means that the thyroid gland follicles overproduce thyroid hormones spontaneously as microautonomous nodules without any extraneous stimuli in the patients with Graves' disease with negative TRAb. But other investigators have not found any definite evidences of this contention and it can be suggested that this controversy will be settled as soon as we understand the exact implications of autoimmune mechanisms in thyroid disease.

We found that 15% of patients with Hashimoto's thyroiditis had positive TBII tests and that 9.5% of Hashimoto's thyroiditis patients had positive TSI activities (Koh 1986). Patients with primary myxedema were shown to have TBII activities in 44% (Koh 1986). Few of normal persons and patients with thyroid carcinoma were found to have TBII activi-

ties of low level. The TBII activities in normal persons have been considered to be caused by non-specifically inhibiting substances in their sera. But Brown and his colleagues (1978) reported that using IgG separated from the sera of normal persons with TSH receptor affinity chromatography they found these IgG's could inhibit the binding of radio-labelled TSH to TSH receptors. And they proposed that TRAb would be usually present in normal persons and that TRAb were not the autoantibodies developed *de novo* in disease state but the products caused by the derangement of normally balanced immune networks. Thus normally occurring TRAb were stressed for their implications in the interpretation of the hypothesis of autoimmunity in terms of idiotype antiidotype interaction.

We have experienced that positive conversion of TBII activity and its return to normal occurred in a patient with subacute thyroiditis (Shong *et al.* 1987a). With increasing activity of TBII the patient became hypothyroid. The generation of cyclic AMP

by cultured FRTL-5 cells was blocked after the addition of the patient's sera collected during the hypothyroid period. Some investigators reported previously that the patients came to have TBII and TSI activities during the transient hyperthyroid period of subacute thyroiditis. With these two findings kept in mind, it can be inferred that the development of TRAb would be explained by the interaction of the environmental challenges and the responses of the immune system and the target gland of the host to these stimuli. Although what are the environmental challenges in the usual cases of Graves' disease are not so well documented as yet we can assume the sequential events of Graves' disease in terms of environment and host interaction as follows; tissue damage by the invasion of the viruses and the release of the autoantigens including TSH receptor antigens and finally the development of the disturbances in the immune system producing autoantibodies. These sequential events are the possible settings for the development and the disappearance of TRAb in its natural progress of disease in subacute thyroiditis and even in Graves' disease. These ideas lead us to study and approach the autoimmune pathogenesis in the thyroid diseases from the viewpoints of the interaction of the host and the environmental pathogens.

6) Clinical features and TSH receptor antibodies

It is now almost certain the TRAb are the cause of the hyperfunctioning thyroid status in Graves' disease. Evidences are as follows; first, almost all of the patients with fresh Graves' disease have TRAb. Second, these antibodies increase the radioactive iodine uptake and release of thyroid hormones by the thyroid follicles *in vitro*, cause the development of colloid droplets within the thyroid follicles, induce glycolysis, increase the activities of adenylate cyclase, and increase the cAMP generation from cultured thyrocytes. Third, the activities of these antibodies and the thyroidal uptake of technetium and the early uptake of radioactive iodine show significant positive correlation. Fourth, the presence of TRAb at the end of antithyroid drug treatment is the prognostic indicator to predict relapse.

According to our observations, TBII activities were high when the goiter was large, and exophthalmopathy was noted more frequently when the TBII activities were very high (Koh 1986, Table 2, Fig. 5). Statistically significant relation of TBII

Table 2. Positive ratios of TBII activities in relation with weight of the thyroid in untreated Graves' disease (Reprinted from Koh C-S. Kor. J. Nuc. Med. 1986, 20:89)

| Weight (gm) | No. of patients | Positive TBII | | Mean TBII activities(%) |
|-------------|-----------------|---------------|-----|-------------------------|
| | | No. | % | |
| <25 | 25 | 18 | 72 | 28.5 |
| 25~50 | 89 | 75 | 84 | 41.7 |
| 50~75 | 53 | 49 | 93* | 49.1* |
| >75 | 29 | 27 | 93* | 56.1* |

*P<0.01 against group whose thyroid is below 25gm.

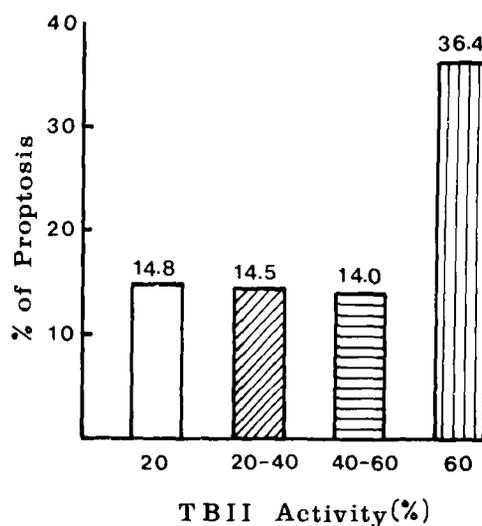


Fig. 5. Prevalences of proptosis with respect to TBII activities in untreated Graves' disease. (Reprinted from Koh C-S. Kor. J. Nuc. Med. 1986, 20:89).

activities with thyroid functional status was observed but the degree of the correlation was not so strong that TRAb measured as TBII activities could not be considered to represent exactly the major factors to bring about the thyroid hyperfunction. Many reports also noticed that serum T3, T4 and radioactive iodine uptake at 24 hours were not related significantly with the titers of TBII. But we observed that the disease relapsed with the rise of the TBII activity during follow-up, in some patients who had been in remission with normalized TBII activities after subtotal thyroidectomy (Oh *et al.* 1987). We suggest this to be the evidence that TRAb would be at least one of the main factors exerting effects on the thyroid function.

7) Changes of TSH receptor antibodies during treatment

a. Antithyroid drug therapy

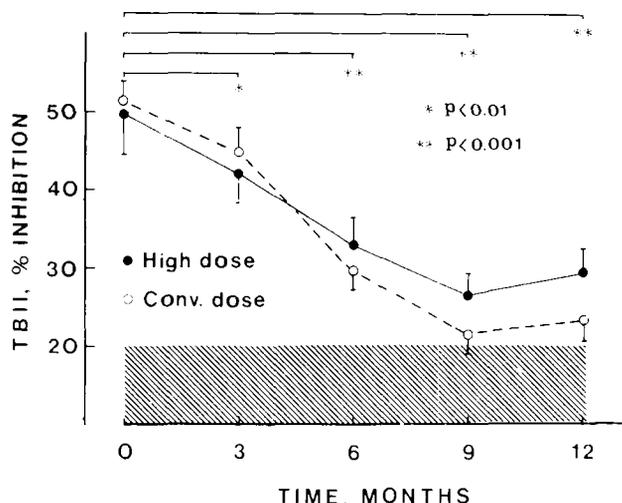


Fig. 6. Changes of TBII activities during high dose (n=26) and conventional dose (n=41) antithyroid drug therapy in 67 patients with Graves' disease. Shaded area represents the normal range. Bars represent S.E.M. (Modified from Moon DH *et al.* Kor. J. Int. Med. 1986, 30:300-307).

The titer of TBII declined from 3 months after administration of antithyroid drugs in Graves' disease patients. The TBII activities at the end of the antithyroid therapy were much lower than the initial titers in the majority of these patients. They were finally normalized in 36% of the patients (Moon *et al.* 1986; Koh 1986, Fig. 6).

It is not certain whether these declines in titer of TRAb is due to the immunosuppressive effects of the antithyroid drugs or to the consequences of the natural course of the disease activities. Although it had been documented that the antithyroid drugs inhibited the thyroid peroxidase, the organification of iodines, and the coupling of iodothyronines, there were also the reports that antithyroid drugs exerted their direct or indirect effects on the immune function of the host. When the antithyroid drugs were added to the culture fluid for lymphocytes from patients with Graves' disease, these drugs were found to decrease the production of immunoglobulin G and antimicrobial antibodies. Increased numbers of activated T lymphocytes in untreated Graves' disease were normalized after the antithyroid drug treatment. The abnormal function of the suppressor T lymphocytes was restored to their normal function after treatment.

We observed such immunomodulatory effects of antithyroid drugs on the development and progres-

sion of experimental thyroiditis. The methimazole pretreated groups of mice had less lymphocytic infiltration and less degree of tissue destruction in the thyroid gland compared with control group when experimental thyroiditis had been induced by immunization with human thyroglobulin and complete Freund's adjuvant. The production of the antibodies decreased to a certain degree in these groups of mice (Kim *et al.* 1987, Table 3). Romaldini and colleagues (1983) reported that the diminution of the TBII activities was more prominent and the remission rates were higher in the patients treated with high dose of antithyroid drugs.

However, Wenzel and Lente (1984) reported that perchlorate administration to the patients with Graves' disease caused the same pattern in decrease of TRAb activities as that found in the patients with antithyroid drug therapy. Moreover, Jansson revealed that the intrathyroidal concentration of thionamide antithyroid drugs *in vivo* was not as high as those used to inhibit the production of immunoglobulins from the patient's lymphocytes cultured *in vitro*.

We evaluated whether the dosage of antithyroid drugs affect the changes of TBII activities in patients with Graves' disease. The modes of the decrease of TBII activities were not different between high dose group and conventional dose group. The decline of TBII activities was found just 3 months after the administration of antithyroid drugs in both groups when the thyroid function were already normalized (Fig. 6, Moon *et al.* 1986). We did not find any difference in the relapse rates between the high dose group and the conventional dose group (Table 4). Even if antithyroid drugs should bring about the decrease of TRAb activities and decrease the degree of tissue damage in experimentally induced thyroiditis, the hypothesis that antithyroid drugs would have immunosuppressive effects on the thyroid autoimmunity needs more amendments and evidences to be verified.

b. ¹³¹Iodine therapy

TRAb activities were reported to rise like the increase of other autoantibodies when radioiodine was administered to patients with Graves' disease. These antibody activities have reached their peaks 2 to 4 months after the administration of radioiodine and the increased activities were again decreased 5 to 9 months after the radioiodine therapy and the TRAb disappeared in the patient's sera 1 year after the therapy (Koh 1986, Fig. 7).

Table 3. Severity of pathologic changes of the thyroid in the mice with experimental thyroiditis in groups; Immunized control group and the groups treated with methimazole and/or thyroxine (Reprinted from Kim MD *et al.* Kor. J. Int. Med. 1987, 32:25)

| Group | Histologic grade(n) | | |
|-------------------|---------------------|------------|--------------|
| | 4 week | 6 week | 8 week |
| Immunized control | 1.5±0.8(8) | 1.4±0.8(7) | 2.1±0.5(8) |
| Immunized/MMI+T4 | 0.8±0.5(8) | 1.3±0.5(8) | 0.9±0.6(9)* |
| Immunized/MMI | | | 1.2±0.5(8)* |
| Immunized/T4 | | | 1.7±0.6(7)** |

(n): Number of mice, MMI: Methimazole

*: p<0.01 between the designated group and immunized control group

** : p>0.1 between the designated group and immunized control group.

Table 4. Relapse and remission rates in patients with Graves' disease treated with high dose and conventional dose of antithyroid drugs (Reprinted from Koh C-S. Kor. J. Nuc. Med. 1986, 20:92)

| Group | No. | Remission | Relapse | |
|-------------------|-----|-----------|-----------|-----|
| High dose | 24 | 9(37.5%) | 15(62.5%) | >NS |
| Conventional dose | 41 | 19(46.3%) | 22(53.7%) | |

NS=Not significant (P>0.05).

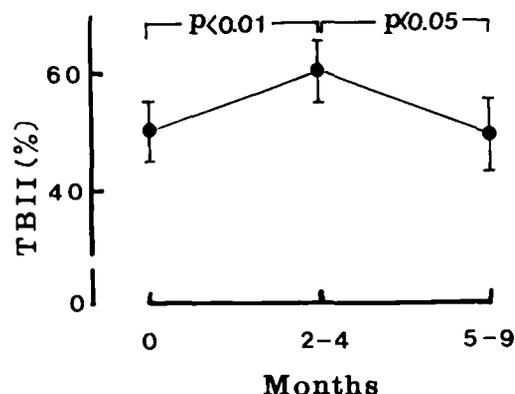


Fig. 7. Changes of TBII activities after ¹³¹Iodine treatment in 39 patients with Graves' disease. Bars represent S.E.M. (Reprinted from Koh C-S. Kor. J. Nuc. Med. 1986, 20:90).

Two hypotheses were proposed for the interpretation of the transient rise of TRAb activities. The first one is that the sensitized suppressor T lymphocytes in the thyroid gland are eradicated earlier than helper T cells because suppressor cells were more sensitive to irradiation from accumulated radioiodine in the thyroid gland. The transient

overproduction of antibody by remaining helper T cells and B cells in the thyroid would then follow. The second explanation is that because of the increase in the release of antigens from the damaged thyroid tissue, the host would produce more auto-antibodies in the thyroid gland.

Some patients with Graves' disease treated with radioiodines show persistently positive TRAb activities when the thyroid functions were normal or sub-normal (Koh 1986). If we admit that TRAb in patients with Graves' disease are the set of polyclonal antibodies with heterogeneous functions, it can be said that stimulating antibodies would disappear after the radioiodine therapy, and blocking or binding-but-not-stimulating antibodies might remain and constitute the remaining TBII activities in the sera of patients in normal or hypothyroid states. But there is an alternate possibility that the thyroid tissue is destroyed by irradiation and thyrocytes or the thyroid follicles, that is, the functional units of the thyroid gland decrease in number. And consequently, these units maintain the functional balance clinically, while they are being stimulated by coexistent stimulating TRAb. The short and long-term influences of radioiodine on the thyroid tis-

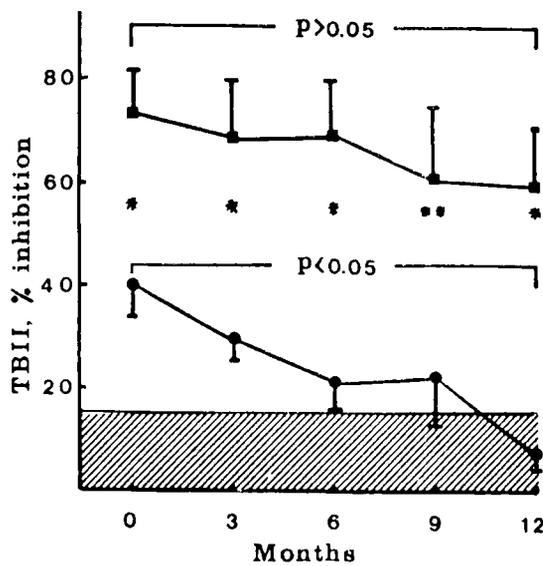


Fig. 8. Changes of TBII activities after subtotal thyroidectomy in decreasing (n=9) and nondecreasing (n=6) groups. Values given are Mean \pm S.E.M.. Shaded area represents the normal range. *, $p < 0.01$ **; $p < 0.05$ between decreasing and non-decreasing groups. (Modified from Oh SK *et al.* J. Kor. Med. Ass. 1987, 30:992).

sues and the immune systems of the patients should be reevaluated in terms of interaction of target tissues and regulatory immune system.

c. Subtotal thyroidectomy

After thyroidectomy, TRAb activities as well as other thyroid autoantibodies begin to decrease from 3 months after operation and these activities disappeared in the sera within a year after the operation. The majority of patients were found to have the persistent negative TBII activities and some of the patients showed again the increase in TBII activities (Oh *et al.* 1987). We found that 60% of 15 cases who were in remission 1 year after thyroidectomy had no detectable TBII activities. And 40% of patients were found to be in clinical remission despite persistently high titers of the TRAb (Fig. 8). The higher titers of TBII these patients have, and the less lymphocyte infiltration in their thyroid glands they have, more likely were they to have elevated TBII activities after thyroidectomy (Fig. 9). With these clinical observations, it was then suggested that the decrease in TRAb activities was more likely due to the decrease in the number of sensitized lymphocytes in the thyroid gland rather than due to the decrease in the antigens residing in the resected mass of the thyroid gland.

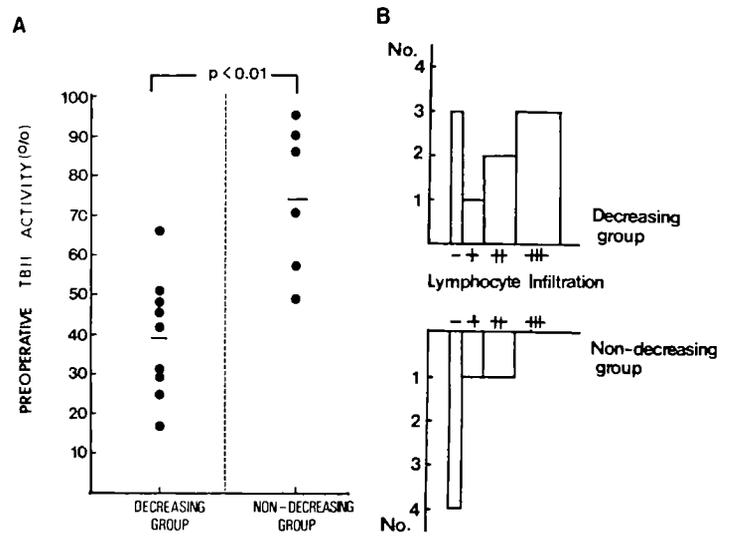


Fig. 9. Preoperative TBII activities in decreasing and non-decreasing groups of Graves' disease patients treated with subtotal thyroidectomy (A) and degrees of lymphocytic infiltration on histopathologic examination of resected thyroid (B) of both groups. (Modified from Oh SK *et al.* J. Kor. Med. Ass. 1987, 30:992-993).

Many authors suggested that the thyroid gland itself was the major production site of TRAb. However, we found no difference between TRAb activities in the peripheral blood and those in thyroidal veins (Oh *et al.* 1986). Lymphocytes taken from lymph nodes and bone marrow were found to have the capability to produce thyroid autoantibodies. These observations support the notion that TRAb are produced in extrathyroidal tissues as well as in the thyroid gland.

The results about the changes of TRAb during and after thyroidectomy did not give definite answers about where the main production site of TRAb was *in vivo* or what were the effects of thyroidectomy upon the aberrant immune balance of autoimmunity. But with the above features of Graves' disease in mind we can come into the tentative conclusion that Graves' disease are the complexes of heterogeneous clinical entities in some of which TRAb are produced mainly in the thyroid gland, and in others these antibodies are produced mainly in the extrathyroidal tissues. The heterogeneity of TRAb in their biologic functions as well as the diversity of the production sites of TRAb are now suspected to be the causes of the various clinical outcomes of the patients with Graves' dis-

Table 5. Remission and relapse with respect to TBII activities at the end of antithyroid drug therapy in 59 patients with Graves' disease (Reprinted from Ihm SH *et al.* Kor. J. Int. Med. 1987, 33:46)

| TBII | Remission | Relapse | Relapse rate* |
|----------|-----------|---------|---------------|
| Negative | 21 | 11 | 34.4% |
| Positive | 5 | 22 | 81.5% |

*; p < 0.001

ease after thyroidectomy. These issues about the heterogeneity of Graves' disease are yet to be clarified.

8) TSH receptor antibodies and the prognosis of Graves' disease

Can TRAb activities be the prognostic indicator when they are measured at the time of withdrawal of the antithyroid drugs? In principle, if TRAb are found after the withdrawal of the antithyroid drugs the activity of the disease is still ongoing and the patient with this antibody will be sure to relapse. But we found that the relapse rate of the patients who still had TBII activities at the end of treatment were 82% (Ihm *et al.* 1987). The patients without TBII were found to be in remission in 65% during 12 months after the withdrawal of drugs. The remaining 35% of the patients relapsed with the simultaneous rise of TBII activities (Table 5). Although the opinions had been prevailing that TRAb could be a good prognostic indicator, we found that there were substantial overlaps in TRAb activities at the end of the antithyroid drug therapy between the relapsed cases and the cases in remission. The positive predictive value of TRAb activities for relapse was about 80% and was similar to that of T3 suppression tests or TRH stimulation tests (Fig. 10).

Using TSI assay methods Zakarija and his colleagues reported that the positive predictive value of TSI was 100% but, thereafter, other groups have reported positive predictive values of 54 to 81% with the similar methods. So even though we had adopted TRAb activities using TSI assay methods to predict the patient's clinical outcome after the drug withdrawal, we were not able to predict the probability of relapse more exactly than we did using TBII assay (Shong *et al.* 1987b).

Although the differences in the groups of patients studied, the duration of treatment, the assay

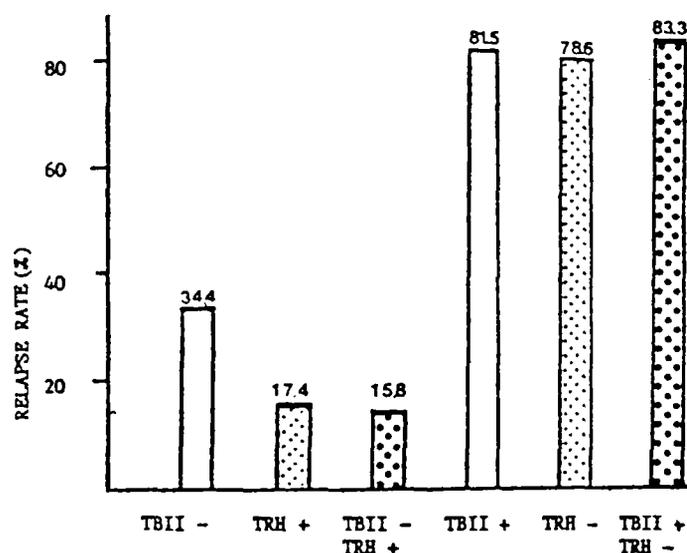


Fig. 10. Relapse rates according to TBII activities at the end of antithyroid drug therapy and TRH responsiveness 3 months after discontinuation of the drugs in patients with Graves' disease. (Reprinted from Ihm SH *et al.* Kor. J. Int. Med. 1987, 33:47).

methods of TRAb, and the follow-up period after treatment could influence the interpretation of the predictive value of these indicators, the measurement of TRAb might be useful to predict the prognosis of a patient instead of cumbersome T3 suppression tests or TRH stimulation tests (Table 6).

Blocking TSH receptor antibody

1) Historical background

In 1978 Endo and Konish found TBII in very high titer in the sera of some patients with primary myxedema. They proved that they were the blocking-type antibodies which could not stimulate the cultured thyrocytes but rather prevent TSH from stimulating the cultured thyrocytes to produce cyclic AMP (Konish *et al.* 1983 & 1985).

In 1980 Matsuura and colleagues reported a case of neonatal transient hypothyroidism born to a mother with primary myxedema. We also have experienced a similar case (Koh 1986). They and we proved the presence of TBII activities in the babies' sera during its hypothyroid period and observed that these babies had recovered from the transient hypothyroid state to normal thyroid function with the disappearance of the TBII. They contended that the hypothyroidism of the baby was due to the transplacental transfer of blocking TRAb. Our case of transient neonatal hypothyroidism due to mater-

Table 6. Predictive values of TBII activities at the end of antithyroid drug therapy, TRH responsiveness 3 months after discontinuation of the drug, and combination of these two (Reprinted from Ihm SH *et al.* Kor. J. Int. Med. 1987, 33:47)

| | % Positive predictive value* | % Negative predictive value** | P value |
|---|------------------------------|-------------------------------|-----------|
| TBII activities at the end of therapy | 81.5(22/27) | 54.6(21/32) | P < 0.001 |
| TRH stimulation test | 78.6(11/14) | 82.6(19/23) | P < 0.001 |
| Combined TRH stimulation test & TBII activities | 83.3(5/ 6) | 84.2(16/19) | P < 0.05 |

*: Positive Predictive value = $\frac{\text{No. of patients with positive test who relapsed}}{\text{No. of patients with positive test}}$

** : Negative Predictive value = $\frac{\text{No. of patients with negative test in remission}}{\text{No. of patients with negative test}}$

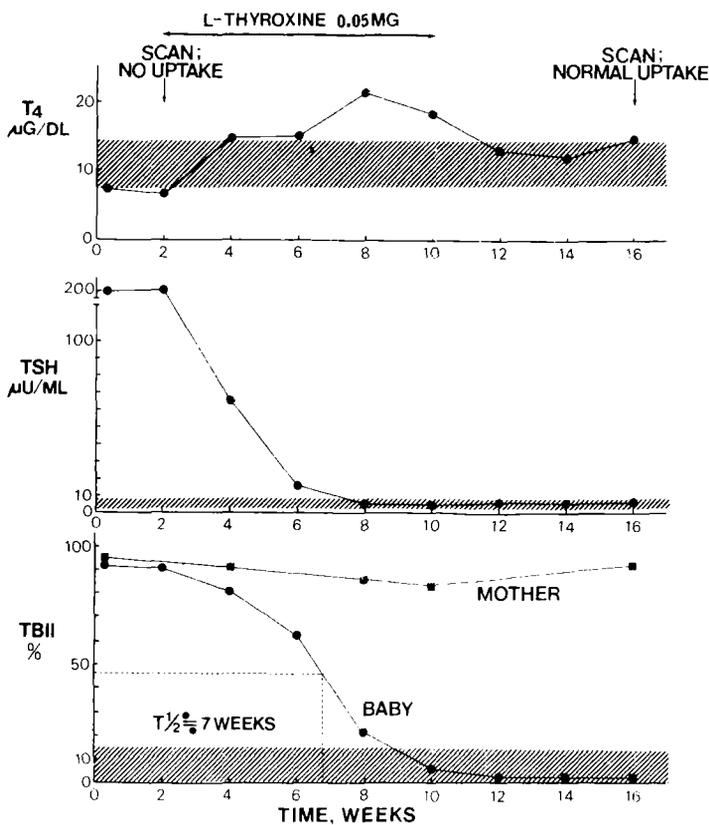


Fig. 11. Serial changes of serum total T4, TSH, and TBII activities of a baby who showed transient hypothyroidism in its neonatal period and serum TBII activities of the mother with primary myxedema with blocking TSH receptor antibodies in her sera. Shaded areas represent normal ranges (Reprinted from Koh C-S. Kor. J. Nuc. Med. 1986, 20:93).

nal blocking TRAb is depicted in Fig. 11.

2) Assay methods and prevalence of blocking TSH receptor antibodies

We observed that 44% of the patients with primary myxedema (11 out of 25 cases since 1984)

had strong TBII activities (Koh 1986). There are few reports of TBII activity in primary myxedema other than ours and those from Konish and his colleagues (1985) who reported prevalence of 25% with TBII activities in primary myxedema. The reports on the myxedema cases with high titers of TRAb have been limited to the above cases from Korea and Japan. And the case reports from the Western countries were very rare. Whether the difference between the different ethnic groups in the prevalence of blocking TRAb are the reality or not and, if it is the case, what are the causes and implications of these differences are to be explained.

With the use of FRTL-5 cell system we assessed the inhibitory action of patient's IgG's on the cAMP generation by TSH (Shong *et al.* 1987c) and named these activities as thyroid stimulating inhibitory immunoglobulins(; TSII). The observed prevalence of TSII activities in the patients with primary myxedema was 75% (21 cases in 28 patients).

3) Characteristics of blocking TSH receptor antibodies

The blocking antibodies which have both TBII and TSII activities are supposed to bind to TSH receptors within the thyroid membranes, to inhibit the binding of TSH, and to block the natural stimuli by TSH from the pituitary. But, so far, it is uncertain whether the binding sites of these antibodies from the patients with primary myxedema are the same as those of the stimulating TRAb from Graves' disease patients.

Kohn and his colleagues reported that the stimulating TRAb bound to the ganglioside portion of the receptor and that the blocking TRAb bound to the

glycoproteins of the receptor (Valente *et al.* 1982). However, Konish and colleagues (1983) and we (Shong *et al.* 1987c) found that immunoglobulins G from the patients with primary myxedema inhibited the stimulating effects of TRAb from the patients with Graves' disease on the cultured thyrocytes. These findings suggest that both kinds of TRAb bind to TSH receptors at the same sites or, at least, at so close domains that allosteric inhibition of binding of stimulating TRAb by blocking TRAb would be possible.

Atrophy of thyroid gland is associated, by definition, with primary nongoitrous myxedema. There was a report that blocking TRAb inhibited the tritiated thymidine uptake by the cultured FRTL-5 cells. The blocking antibodies are now suspected to inhibit the growth stimulating effect of TSH and to cause the atrophy of the thyroid in turn.

The following problems about blocking TRAb remain to be solved in the near future; clinical significance of blocking TRAb in primary myxedema, the pathophysiology of primary myxedema with negative TRAb, the relationship of the blocking TRAb and the stimulating TRAb in terms of the polyclonal functional heterogeneity and of the interaction of these antibodies with TSH receptors, and the significance of TRAb operating as the goitrogen or the inducer of atrophy of the thyroid gland.

Anti-TSH antibody

Since the radioreceptor assays measuring TRAb activities are being performed routinely, there have been a few reports of anti-TSH antibodies in the sera of the patients with Graves' disease. These antibodies were noticed incidentally since the radioactivity counts in the bound fraction precipitated by polyethylene glycol during the radioreceptor assay of TBII were absurdly high, compared with the binding efficiency of radiolabelled bovine TSH to the solubilized receptor. These antibodies were reported not to interfere with TSH radioimmunoassay or TSH immunoradiometric assay but to interfere with TRAb radioreceptor assay. This observation led the investigators to speculate that these antibodies are against the epitopes of TSH which are equal to the binding sites for the TSH receptor within the thyroid membrane (Kajita *et al.* 1983; Akamizu *et al.* 1984; Raines *et al.* 1985).

We also observed the cases with anti-TSH antibodies in 3 patients with Graves' disease and in 1 patient with primary myxedema (Fig. 12, Cho *et al.*

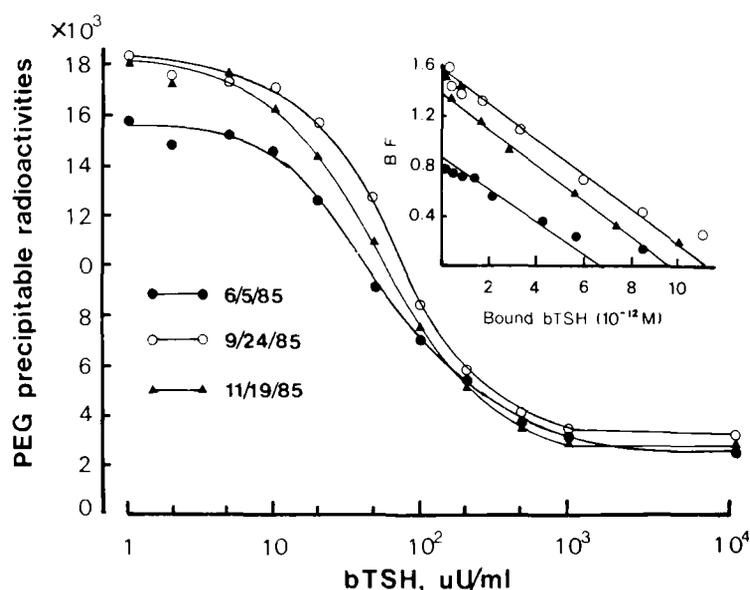


Fig. 12. Displacement of PEG precipitable ^{125}I -bTSH binding of IgGs of a patient with Graves' disease by bTSH. The insert shows Scatchard plot of bTSH binding to patient IgG. (PEG; polyethylene glycol, bTSH; bovine TSH. Reprinted from Cho BY *et al.* In *Recent Progress In Thyroidology*. 1987b, p313).

1986b, 1987a & b). The presence of anti-TSH antibodies in the above two types of the autoimmune thyroid diseases associated with TRAb evoked again the interests in the idiotype and antiidiotype network hypothesis of autoimmunity as common mechanism of pathogenesis of these two diseases. Unknown host or environmental factors would induce autoantibodies against TSH. The following development of antiidiotype antibodies against these antibodies would crossreact with TSH receptors within the thyrocyte membrane, mimicking the binding sites of TSH which bind to and stimulate TSH receptors.

But the prevalence of these anti-TSH antibodies was so low in Graves' disease patients that anti-TSH antibodies may not be interpreted to have any significance in the pathogenesis of autoimmune thyroid diseases in general. Now it is more likely that anti-TSH antibodies are produced in the patients with autoimmune thyroid diseases as a byproduct of disordered immune tolerance to thyroid membrane antigens. Besides, when we used human TSH to displace the radiolabelled bovine TSH from binding to patient's IgG's, bovine TSH was not displaced from the patient's IgG's by human TSH, also suggesting that anti-TSH antibodies in the autoimmune thyroid diseases are the products of the

epiphenomenon of the disordered immune tolerance (Cho *et al.* 1987a).

Cellular Immunity

Lymphocytes in thyroid glands

The number of lymphocytes in the thyroid gland in Graves' disease and Hashimoto's thyroiditis were found to be increased. The majority of the infiltrated lymphocytes were reportedly T lymphocytes. In the patients with the above diseases, T/B ratio of lymphocytes in the thyroid glands was higher than that of lymphocytes in peripheral blood. According to the reports of Margolick and colleagues (1984), T lymphocytes around the follicular epithelial cells were mainly suppressor T lymphocytes and helper T cells gathered in the interfollicular spaces. The reports on the proportion of suppressor and helper T cells infiltrated in the thyroid gland was quite different from one authority to another. The lymphocytes infiltrating the thyroid gland were counted as being in an activated state. B lymphocytes in the thyroid tissue showed more likelihood to produce the antibodies spontaneously *in vitro* without extraneous stimuli. More Ia positive T lymphocytes were found in the thyroid gland than in peripheral blood in patients with autoimmune thyroid diseases. These reports suggested that B and T lymphocytes in the thyroid gland were activated ones and were in sensitized state against the thyroid autoantigens. It is more likely for these cells to produce any autoantibodies against thyroid antigens while the autoantigens on the thyrocyte membranes are being presented to these lymphocytes.

It has been observed that normal epithelial cells express only class 1 molecules on their surface membranes and if the epithelial cells would express class 2 molecules they could present their surface antigens to their autologous lymphocytes (Londei *et al.* 1984). Recently Bottazzo and his colleagues (1983) reported that the thyrocytes of the patients with autoimmune thyroid diseases expressed aberrantly HLA DR antigens and that the thyrocytes would express HLA DR antigens if they were stimulated by lectins or gamma interferon, as was the case with our experience (Lee *et al.* 1987). They also clarified that T lymphocytes infiltrating the thyroid gland in Graves' disease expressed HLA DR antigens and that the clones which would adhere to the DR expressing thyrocytes were included among these T cells (Londei *et al.* 1985).

We confirmed that cultured normal thyrocytes

expressed DR antigens when they were stimulated with PHA, Con A, LAG and gamma interferon (Lee *et al.* 1987). Hence, for the time being, it can be stated that the main pathology in the thyroid gland is brought about through the aberrant interactions of the sensitized and activated Ia positive T lymphocytes and the thyrocytes which expressed class 2 molecules.

Lymphocytes in peripheral blood

1) Population of lymphocytes

The reports on the population of lymphocytes in the peripheral blood of the patients with autoimmune thyroid diseases were much different in composition from those of normal persons from one investigator to another. The numbers of B lymphocytes in the peripheral blood were reportedly within normal limits. But there has been no agreement about the numbers of T lymphocytes in the peripheral blood, that is, many reports said that the counts of T cells were normal, increased or decreased. Besides, the reports on the proportion and numbers of the helper and suppressor lymphocytes among T cell population were much different. The diversity of the results about the counts of lymphocytes from different investigators is considered to be due to the following reasons; the different experimental methods of counting lymphocytes, variable influences on the counts emanating from the non-immunologic causes such as adrenergic tones of the individual, and the effects of antithyroid drug therapy at the time of blood withdrawal.

2) Functions of lymphocytes

If thyroid antigens such as thyroid cell membrane or thyroglobulin are added to the cultured lymphocytes of the patients with Graves' disease or Hashimoto's thyroiditis, the lymphocytes are reportedly to develop blastogenesis and to produce thyroid autoantibodies. And these lymphocytes were observed to be able to produce antithyroglobulin antibodies or TSH receptor antibodies when they were stimulated with pokeweed mitogen. This means that the lymphocytes in the peripheral blood in the patients are functionally replete and have already been sensitized specifically against the thyroid autoantigens. According to Kidd's observations (1980), T lymphocytes drawn from the patients with Graves' disease or Hashimoto's thyroiditis could produce migration inhibition factors (MIF) if they were challenged with crude extracts of thyroid tissues or solubilized TSH receptors. But if these cells were incubated with normal T lympho-

cytes, they were not able to produce MIF. These findings imply that the B cells and helper T cells in those patients have already been sensitized against thyroid antigens and that suppressor T lymphocytes were functionally repressed.

3) Abnormalities of suppressor T lymphocytes

There is much experimental evidence about the functional abnormalities of suppressor T lymphocytes. Pacini and DeGroot (1983) observed that the production rate of IgG's by the mixtures of T and B lymphocytes drawn from normal persons increased progressively until the ratio of B and T lymphocytes became 1:4 and then decreased after the ratio of B and T cells was over 1:4. To the contrary, when the mixtures of the lymphocytes drawn from the patients with Graves' disease were used, the production rate of IgG's increased continuously until the ratio of B and T lymphocytes was more than 1:10. If B lymphocytes from Graves' disease patients and T lymphocytes from normal persons were mixed, the production of immunoglobulins was suppressed when the ratio was over 1:4. If B lymphocytes from normal persons and T lymphocytes from Graves' disease patients were mixed then the suppression of the immunoglobulin production was not observed. With these observations they suggested that the dysfunction of suppressor T lymphocytes were important as a pathogenetic mechanism in Graves' disease.

Okita and his colleagues (1981) presented further evidence about the dysfunction of suppressor T lymphocytes in autoimmune thyroid diseases with the assay system of MIF production. They observed that the production of MIF in response to thyroid antigens was suppressed if T lymphocytes from normal persons were added to T lymphocytes from the patients with Graves' disease or Hashimoto's thyroiditis. With the same experimental system, Topliss (1983) confirmed that a similar defect in the suppression of MIF production could be induced if T lymphocytes from normal subjects had been irradiated before these cells were added to the T cells from normal subjects or patients with autoimmune thyroid diseases.

These defects in the suppressor function of lymphocytes have been supposed to be antigen-(organ-) specific and the experimental evidences about these contentions are being accumulated. According to the data of Topliss and his colleagues (1983), T lymphocytes from the patients with insulin de-

pendent diabetes mellitus (IDDM) can produce MIF by the challenge of islet cells and T cells from the patients with Graves' disease, but did not produce MIF by the challenge of islet cells. When T lymphocytes from Graves' disease patients were added to the T cells from IDDM patients, the production of MIF by T lymphocytes from IDDM patients challenged by islet cells was suppressed. They concluded with these findings that the organ specificity of autoimmune diseases was due to the antigen specific defects in suppressor T lymphocytes. Noma and colleagues (1982) reached the same conclusion through the analysis of the regulatory mechanism of lymphocytes with plaque forming cell assay for antithyroglobulin antibodies.

Immunogenetic Influences

Genetic background

Genetic influences upon the pathogenesis of the autoimmune thyroid diseases have been well known for the past 20 years. According to the previous studies, about 7 to 27% of the relatives of the patients with Graves' disease showed the abnormalities in their thyroid functions and 4 to 6% of the female persons and 1% of male persons among the parents and siblings of the probands were reported to have Graves' disease.

Tamai and his colleagues (1980) performed T3 suppression tests and TRH stimulation tests in 206 relatives of the patients with Graves' disease and found that 27.1% of the subjects gave abnormal test results (no response of stimulation in 14% and hyperresponsiveness in 13.1%) and that in 6.8% of the subjects radioactive iodine uptake could not be suppressed after T3 administration. They followed 69 of the persons with abnormal results and found that 3 of them developed hyperthyroidism and 2 of them developed hypothyroidism within 18 months of follow-up period. The fact that the coincidence of Graves' disease was 5% in heterozygous twins, but the coincidence was 50% in homozygous twins and also suggests the importance of the genetic predisposition for the development of autoimmune thyroid diseases.

The prevalence of Hashimoto's thyroiditis was higher in certain families and about 50% of the relatives of the patients with Hashimoto's thyroiditis were found to have thyroid autoantibodies. Burek and colleagues (1982) found that among the unaffected children of the parents both of whom had autoimmune thyroid diseases, the prevalence of the thyroid autoantibodies was higher than that

Table 7. HLA-DR antigen frequencies in Korean patients with Graves' disease and controls (Reprinted from Cho BY *et al.* Tissue Antigens 1987c, 31:120)

| HLA | Antigen frequencies (%) | | RR | EF (PF) | χ ² | P | CP |
|------|-------------------------|-------------------|-----|------------|----------------|---------|-------|
| | Patients n=128 | Controls n=220 | | | | | |
| DR1 | 4.7 | 8.2 | 0.6 | (0.04) | 1.54 | 0.21 | NS |
| DR2 | 33.6 | 34.5 | 1.0 | (0.01) | 0.03 | 0.86 | NS |
| DR3 | 9.4 | 2.7 | 3.7 | 0.07 | 7.29 | 0.007 | NS |
| DR4 | 36.7 | 37.7 | 1.0 | (0.02) | 0.04 | 0.85 | NS |
| DR5 | 17.2 | 4.5 | 4.4 | 0.13 | 15.49 | 0.00008 | 0.007 |
| DRw6 | 9.4 | 20.5 | 0.4 | (0.12) | 7.25 | 0.007 | NS |
| DR7 | 2.3 | 3.6 | 0.6 | (0.01) | 0.44 | 0.50 | NS |
| DRw8 | 29.7 | 15.5 | 2.3 | 0.17 | 9.99 | 0.002 | 0.02 |

RR: Relative risk, EF: Etiologic fraction, PF: Preventive fraction (if RR < 1)

CP: Corrected P value (P x No. of tested antigens), NS: Not significant

EF=(RR-1)×antigen frequency/RR

$$PF = \frac{(1-RR) \times \text{antigen frequency}}{RR \times (1-\text{antigen frequency}) + \text{antigen frequency}}$$

among the unaffected children of the parents only one of whom had the diseases and of the parents neither of whom had autoimmune thyroid diseases. The above results from the family studies indicate the existence of the genetic predisposition in some patients and families to autoimmune thyroid diseases.

Immunogenetic influences

It has been well recognized that the close relationship could be found between HLA antigenic phenotypes and Graves' disease and this was considered as an evidence for the hypothesis that the aberrations in the immune tolerance had been derived from the immunogenetic constitution of an individual. The allelic associations of HLA phenotypes with Graves' disease were reported so differently from one authority to another according to the ethnic background of the studied subjects. In Caucasians, the phenotypes of B8 and DR3, B35, DR5 and Dw12 in Japanese, and Bw46 and DR5 in Chinese were reported to be closely related with Graves' disease (Cho 1987d). We found that the prevalence of B13, DR5 and DR8 was significantly higher in Korean patients with Graves' disease compared with normal controls, but that the etiologic fraction of these antigens were not so high that the possibility of the significant contribution of these antigens to the development of Graves' dis-

ease in a population could be denied (Table 7, Cho *et al.* 1987c). But, of course, in Caucasians B8 and DR3 prevalence in general population and then the etiologic fraction of these antigens among patients' group were high and these antigens could be considered as one of the major contributing etiologic factors in the majority of the Graves' disease patients. Besides, some of the investigators could find relatively good predictive value of these antigens for the prediction of the relapse or remission.

The phenotypes of HLA antigens and the clinical findings such as the age of onset, sex, family history, the weight of goiter, the severity of exophthalmopathy, the titers of autoantibodies, and the initial TSH receptor antibody activities was not correlated and so the factors determining the clinical features of patients and their immunogenetic backgrounds are not considered as being concerned with each other so closely (Cho *et al.* 1987c). Though some of the investigators reported that the phenotypes of HLA antigens would be the prognostic indicator to predict the relapse or remission of patients, we could not find in Koreans any of the HLA phenotypes, as being the good indicator of prognosis, which was the case with the reports of Allanic and others (1983).

In the case of Hashimoto's thyroiditis the disease association with HLA phenotypes has not been

thought to be so strong and only weak association with HLA DR5 was reported. In Caucasians, the disease association of HLA phenotypes in primary myxedema was similar to that in Graves' disease.

Burek and colleagues (1984) studied the prevalence of thyroid autoantibodies and that of subclinical thyroid diseases in the siblings of the patients with Hashimoto's thyroiditis (age: 8-16) with relation to HLA haplotype identity. 90% of siblings had antithyroid autoantibodies when the HLA haplotypes were identical, but 70% and 50% of siblings had the antibodies when only one locus was matched or there was no identity in haplotypes, respectively.

The suggested mechanisms of the disease association with HLA antigens in autoimmune thyroid diseases are as follows: first; the linkage disequilibrium of the HLA genes and disease susceptibility genes, second; structure-function relationships of class 1 and class 2 molecules involved in the cellular interactions. More clinical data and the well-organized experimental researches are required before we can get to the point in this aspect.

In conclusion, the disease association of HLA phenotypes can be interpreted as an indicator of the immunogenetic predisposition to the development of disordered immune tolerance. The properties of HLA antigens expressed on the cell membranes of the host cells and regulatory immunocytes would operate as important bases for the development of autoimmunity. But, so far, the antigenic phenotypes in patients with autoimmune thyroid diseases are not considered to be a factor to give direct influences on the diversity of clinical features.

Suggested Mechanisms of Autoimmunity in Thyroid Diseases

The mechanisms of the development of the thyroid autoantibodies in autoimmune thyroid diseases are not clarified yet. It is expected that many research works and efforts based on the recent developments of immunology will be able to elucidate the exact mechanisms and their implications in the interpretation of clinical features of the autoimmune thyroid diseases. Previously suggested mechanisms about the pathogenesis of the autoimmune thyroid diseases can be summarized as follows (Cho 1987d); four hypotheses that are closely related with the general theory of the pathogenesis of the autoimmune diseases.

Table 8. Distribution of HLA-DR5 with respect to remission and relapse in patients with Graves' disease (Modified from Cho BY *et al.* Tissue Antigens 1987c 31:120)

| HLA-DR | Remission | Relapse | Relapse Rate |
|----------|-----------|---------|--------------|
| Positive | 6 | 5 | 45% |
| Negative | 18 | 25 | 58% |
| Total | 24 | 30 | |

Disordered functions of antigen specific suppressor T lymphocytes

As one grows older, various environmental factors induce the lymphocytes by somatic mutation which are reactive with the autoantigens. In normal subjects, suppressor T lymphocytes against the abnormal self-reactive lymphocytes come out and eradicate these clones of lymphocytes by their immune surveillance effects. But in the affected persons with autoimmune thyroid diseases the self-reactive clones proliferate and produce autoantibodies probably due to the functional abnormalities of the specific suppressor T lymphocytes. It is well known that the suppressor T lymphocytes of the patients with autoimmune thyroid diseases have quantitative and qualitative defects (Strakosch *et al.* 1982), but there has been no report on the evidences that the abnormal clones are produced via the mechanism of somatic mutation being related with the dysfunction of the suppressor T lymphocytes.

HLA-DR antigenic expression of the thyrocytes

Helper T lymphocytes should recognize antigens to help B cells produce antibodies and this antigenic recognition is restricted by HLA-DR antigens on the cell surface. Only when class 2 HLA antigens are co-presented with the self or non-self antigens to helper T lymphocytes, these helper T cells begin to proliferate and stimulate B lymphocytes to produce autoantibodies. Recently Bottazzo's group (1983) reported that HLA DR antigens were expressed on the surface membrane of thyrocytes of the patients with autoimmune thyroid diseases and that the presentation of these class 2 molecules could be induced by gamma interferon. The following reports from this group (Londei *et al.* 1984 & 1985) manifested that DR antigen expressing epithelial cells induced proliferation of the auto-

logus T lymphocytes and that the T lymphocyte clones from the patients with autoimmune thyroid diseases were specifically reactive with autologous thyrocytes and adhered to these cells.

It is deducible now that gamma interferon produced by T lymphocytes through environmental stimuli such as viral infections stimulates the thyrocytes to express HLA DR antigens and that helper T lymphocytes recognize the autoantigens on the surface membrane of the thyrocytes coincidentally with the class 2 molecules, so as to make T and B cells proliferate and to help B lymphocytes to produce autoantibodies. Even in normal persons, T lymphocytes reactive with autoantigens were reported to be present in peripheral blood, warranting the validity of this hypothesis. But it is still uncertain whether DR expression of the thyrocytes are the causative factor of disease development or the secondary phenomenon to the disease process, and what are the primary causes to induce the DR antigenic expression.

Idiotype-antiidiotype interaction

TRAb are being produced by self-reactive clones even to be documented in peripheral blood of normal healthy persons. In normal persons, these self-reactive antibodies are under the control of anti-idiotype antibodies, to be neutralized by anti-idiotype antibodies. But in patients with Graves' disease TRAb are being produced continuously due to the disordered regulation of idiotype-antiidiotype network. This is one of the interpretations about the pathogenetic mechanisms under the hypothesis of idiotype-antiidiotype network in immune balance. On the other hand, autoantibodies against thyroid stimulating hormones are produced by unknown environmental influences, to induce the production of the antiidiotype antibodies the structure of which is very similar to the epitopes of TSH in order to mimic TSH action on the TSH receptors within the thyrocyte membrane. Recent elucidation of the presence of anti-TSH antibodies in a few patients with Graves' disease or primary myxedema (Cho *et al.* 1987b) evoked much interests in this hypothesis, but the lowest prevalence, if ever, of anti-TSH antibodies in Graves' disease patients aroused skepticism about the generalization of this mechanism to every case of Graves' disease.

Cross reaction

Ingbar and colleagues (1983) proposed that TSH

receptor antibodies would be produced by environmental stimuli in Graves' disease, reporting that TSH receptors were found in the cell membranes of *Yersinia enterocolitica* and *E coli* and that cross-reacting antibodies with the antibodies against TSH receptors on these bacterial cell walls were likely to come to act as autoantibodies to cause the hyperthyroid function in patients.

SUMMARY

For the past 30 years, autoimmune mechanism has been thought to be involved in the pathogenesis of thyroid diseases, while a lot of phenomena of impaired tolerance to self antigens in thyroid disease patients have been revealed. Autoantibodies to every kind of thyroid related antigens have been found, at least in some of the patients with autoimmune thyroid diseases.

The author has discussed the autoantibodies against thyroid specific antigens thoroughly, to elucidate the pathophysiologic significance of humoral immunity in the genesis of autoimmune thyroid diseases. Among these, the discussion about TSH receptor antibodies was more concrete, to present the importance of the stimulating effects of TSH binding inhibitory immunoglobulins on the thyroid function and to compare these effects with those of blocking-type TBII's frequently observed in the patients with primary myxedema.

Cellular immunity in autoimmune thyroid diseases was then discussed in the aspects of an independent contribution to autoimmune pathogenesis in thyroid diseases and an interrelation with humoral immunity, and as a further basis for the induction and maintenance of the disordered humoral immunity in thyroid disease patients. The discoveries about the immunogenetic background of the patients with autoimmune thyroid diseases were described and their roles in autoimmune pathogenesis in thyroid diseases were mentioned. With the results in mind, suggested mechanisms of autoimmune pathogenesis in thyroid diseases were briefly discussed.

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REFERENCES

- Adams DD, Purves DD.** Abnormal responses in the assay of thyrotrophin. *Proc. Univ. Otago. Med. School.* 1956, 34:11-16
- Adams DD, Kennedy TH.** Evidence to suggest that LATS protector stimulates the human thyroid gland. *J. Clin. Endocrinol. Metab.* 1971, 33:47-51
- Ahn I-M, Cho BY, Koh C-S, Lee M, Park SH, Kim YI.** Immunofluorescent findings in Graves' disease and Hashimoto's disease. *Seoul J. Med.* 1985, 26:149-156
- Akamizu T, Ishii H, Mori T, Ishihara T, Ikekubo K, Imura H, Bito S, Saiki Y.** Abnormal thyrotropin-binding immunoglobulins in two patients with Graves' disease. *J. Clin. Endocrinol. Metab.* 1984, 59:240-245
- Allanic H, Fauchet R, Lorcy Y, Guerguer B, LeGuerrier A-M, Genetet B.** A prospective study of the relationship between relapse of hyperthyroid Graves' disease after anti-thyroid drugs and HLA haplotypes. *J. Clin. Endocrinol. Metab.* 1983, 57:719-722
- Bottazzo GF, Pujol-Borrell R, Hanafusa T, Feldmann M.** Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. *Lancet* 1983, 2:1115-1119
- Brown RS, Jackson IM, Pohl SL, Reichlin S.** Do thyroid-stimulating immunoglobulins cause non-toxic and toxic multinodular goiter? *Lancet* 1978, 1:904-906
- Burek CL, Hoffman WH, Rose NR.** The presence of thyroid autoantibodies in children and adolescents with autoimmune thyroid disease and in their siblings and parents. *Clin. Immunol. Immunopathol.* 1982, 25:395-404
- Burek CL, Rose NR, Najjar GM, Gimelfarb A, Zmijewski CM, Polesky HF, Hoffman WH.** In Panayi GS, David CS (Ed) *Immunogenetics.* Butterworth, London, 1984, pp. 207-215
- Cho BY, Koh C-S, Lee M.** Clinical significance of the TSH-binding inhibiting immunoglobulins(TBII) assay in patients with autoimmune thyroid diseases. *Kor. J. Int. Med.* 1985a, 28:299-308
- Cho BY, Koh EM, Chung MH, Koh C-S, Min HK, Lee M.** Significances of blocking TSH receptor antibody and effect of steroid therapy in primary myxedema. *Kor. J. Int. Med. (Abstr. 37)* 1985b, p207
- Cho BY.** Autoimmune pathogenesis in thyroid diseases. *J. Kor. Med. Ass.* 1985c, 28:713-720
- Cho BY, Choe SJ, Koh C-S, Lee M.** Anti-thyroxine antibodies in autoimmune thyroiditis-effect on radioimmunoassay and binding characteristics. *Kor. J. Int. Med.* 1986a, 1:7-13
- Cho BY, Chung JH, Choe SJ, Kim SY, Lee HK, Koh, C-S, Min HK, Lee M.** A study for the relationship of anti-TSH antibody and TSH receptor antibody. *Kor. J. Int. Med. (Abstr. 38)* 1986b, p233
- Cho BY, Choi CW, Koh C-S, Min HK, Lee M.** Characteristics of anti-TSH antibody in Graves' disease patients. *Kor. J. Int. Med. (Abstr. 39)* 1987a, p206
- Cho BY, Lee HK, Koh C-S, Min HK, Lee M.** Anti-TSH antibodies in patients with Graves' disease and primary nongoitrous myxedema. In Vichayanrat A, Nitiyanant W, Eastman C, Nagataki S(Ed) *Recent Progress In Thyroidology.* Cyrstall house press, Bangkok, 1987b, pp310-316
- Cho BY, Rhee BD, Lee DS, Lee MS, Kim GY, Lee HK, Koh C-S, Min HK, Lee M.** HLA and Graves' disease in Koreans. *Tissue Antigens* 1987c, 31: 119-121
- Cho BY.** Autoimmune thyroid disease. *J. Kor. Soc. Endocrinol.* 1987d, 2:101-122
- Chung JH, Lee MS, Cho BY, Lee HK, Koh C-S, Min HK, Lee M.** The analysis of the value of the thyroid autoantibody measured by radioimmunoassay. *Kor. J. Nuc. Med.* 1987, 21:133-141
- Endo K, Kasagi K, Konish J, Ikekubo K, Okuno T, Takeda Y, Mori T, Torizuka K.** Detection and properties of TSH-binding inhibitor immunoglobulins in patients with Graves' disease and Hashimoto's thyroiditis. *J. Clin. Endocrinol. Metab.* 1978, 46:734-739
- Hay FC, Torrigina G.** The distribution of antithyroglobulin antibodies in the immuoglobulin G subclasses. *Clin. Exp. Immunol.* 1973, 15:517-520
- Ihm SH, Cho BY, Lee HK, Koh C-S, Min HK, Lee M.** Prognostic value of TSH receptor antibodies and TRH stimulation test in patients with Graves' disease after longterm treatment with antithyroid drugs. *Kor. J. Int. Med.* 1987, 33:44-52
- Jansson R, Dahlberg PA, Johansson H, Lindstrom B.** Intrathyroidal concentrations of methimazole in patients with Graves' disease. *J. Clin. Endocrinol. Metab.* 1983, 57:129-132
- Kajita Y, Nakajima Y, Ishida M, Ochi Y, Miyazaki T, Hachiya T, Ijichi H.** Characteristics of auto-antibodies to bovine TSH in the serum of two patients with Graves' disease. *Acta Endocrinol.* 1983, 104:423-430
- Karlsson FA, Wibell L, Wide L.** Hypothyroidism due to thyroid-hormone-binding antibodies. *N. Engl. J. Med.* 1977, 296:1146-1148
- Kidd A, Okita N, Row VV, Volpe R.** Immunologic aspects of Graves' and Hasimoto's disease. *Metabolism* 1980, 39:80-86
- Kim MD, Ihm SH, Lee DS, Cho BY, Lee HK, Koh C-S, Suh EH, Kim CW, Kim YI.** Immunosuppressive effect of methimzaole (1-methyl-2-mercaptoimidazole)

- on experimental thyroiditis of mouse. *Kor. J. Int. Med.* 1987, 32:20-30
- Koh C-S.** The roles of the TSH receptor antibodies in autoimmune thyroid diseases. *Kor. J. Int. Med.* 1986, 20:85-100
- Konish J, Iida Y, Endo K, Misaki T, Nohara Y, Matsuura N, Mori T, Torizuka K.** Inhibition of thyrotropin-induced adenosine 3',5'-monophosphate increase by immunoglobulins from patients with primary myxedema. *J. Clin. Endocrinol. Metab.* 1983, 57:544-549
- Konish J, Iida Y, Kasagi K, Misaki T, Nakashima T, Endo K, Mori T, Shinpo S, Nohara Y, Matsuura N, Torizuka K.** Primary myxedema with thyrotropin-binding inhibitor immunoglobulins. Clinical and laboratory findings in 15 patients. *Ann. Int. Med.* 1985, 103:26-31
- Lee MS, Lee DS, Han JS, Cho BY, Koh C-S, Lee M.** The prevalence of antithyroid autoantibodies in normal Korean population—age, sex distribution and its relation to thyroid function. *Kor. J. Int. Med.* 1986, 1:31-36
- Lee MS, Lee CK, Shong YK, Cho BY, Lee HK, Koh C-S, Min HK, Lee M, Oh SK, Whang ES, Cha CY.** The effects of immune modifiers on the HLA-DR antigen expression of the cultured thyrocytes. *Kor. J. Int. Med.* (Abstr. 39) 1987, p191
- Lee MS, Shong YK, Cho BY, Lee HK, Koh C-S, Min HK, Lee M, Oh SK, Whang ES, Cha CY, Park SH, Lee CK.** HLA-DR antigen expression on the thyrocytes of Graves' disease. *Kor. J. Int. Med.* 1988 (in press)
- Londei M, Lamb JR, Bottazzo GF, Feldmann M.** Epithelial cells expressing aberrant MHC class II determinants can present antigen to cloned human T cells. *Nature* 1984, 312:639-641
- Londei M, Bottazzo GF, Feldmann M.** Human T-cell clones from autoimmune thyroid glands: specific recognition of autologous thyroid cells. *Science* 1985, 228:85-89
- Margolick JB, Hsu SM, Volkman DJ, Burman KD, Fauci AS.** Immunohistochemical characterization of intrathyroid lymphocytes in Graves' disease. Interstitial and intraepithelial populations. *Am. J. Med.* 1984, 76:815-821
- Mariotti S, Anelli S, Ruf J, Bechi R, Czarnocka B, Lombardi A, Carayon P, Pinchera A.** Comparison of serum thyroid microsomal and thyroid peroxidase autoantibodies in thyroid diseases. *J. Clin. Endocrinol. Metab.* 1987, 65:987-993
- Matsuura N, Yamada Y, Nohara Y, Konishi J, Kasagi K, Endo K, Kojima H, Witaya K.** Familial neonatal transient hypothyroidism due to maternal TSH-binding inhibitor immunoglobulins. *N. Eng. J. Med.* 1980, 303:738-740
- Moon DH, Suh K, Cho BY, Koh C-S, Min HK, Lee M.** Changes of TSH receptor antibodies in Graves' disease during treatment with antithyroid drugs—its relation to dose and duration of treatment and clinical features. *Kor. J. Int. Med.* 1986, 30:300-307
- Mori T, Kriss JP.** Measurements by competitive binding radioassay of serum antimicrosomal and anti-thyroglobulin antibodies in Graves' disease and other thyroid disorders. *J. Clin. Endocrinol. Metab.* 1971, 33:688-698
- Noma T, Yata J, Shishiba Y, Inatsuki B.** *In vitro* detection of anti-thyroglobulin antibody forming cells from the lymphocytes of chronic thyroiditis patients and analysis of their regulation. *Clin. Exp. Immunol.* 1982, 49:565-571
- Nye L, Decarvalho LP, Roitt IM.** Restriction in the response to autologous thyroglobulin in the human. *Clin. Exp. Immunol.* 1980, 41:252-263
- Oh SK, Kim JP, Kim SE, Cho BY, Koh C-S, Kim CW.** Difference of TSH receptor antibodies in thyroidal veins and peripheral blood, and changes of TSH receptor antibody activities after subtotal thyroidectomy in patients with Graves' disease. *J. Kor. Med. Ass.* 1987, 30:990-998
- Okita N, Row VV, Volpe R.** Suppressor T lymphocyte deficiency in Graves' disease and Hashimoto' thyroiditis. *J. Clin. Endocrinol. Metab.* 1981, 52:528-533
- Pacini F, DeGroot LJ.** Studies of immunoglobulin synthesis in cultures of peripheral T and B lymphocytes: Reduced T-suppressor cell activity in Graves' disease. *Clin. Endocrinol.* 1983, 18:219-232
- Raines KB, Baker JR, Lukes YG, Wartofsky L, Burman KD.** Antithyrotropin antibodies in the sera of Graves' disease patients. *J. Clin. Endocrinol. Metab.* 1985, 61:217-222
- Roitt IM, Doniach D, Campbell PN, Hudson RV.** Autoantibodies in Hashimoto's disease (lymphadenoid goitre). *Lancet* 1956 2:820-821
- Romaldini JH, Bromberg N, Werner RS, Tanaka LM, Rodrigues HF, Werner MC, Farah CS, Reis LC.** Comparison of effects of high and low dosage regimens of antithyroid drugs in the management of Graves' hypertyroidism. *J. Clin. Endocrinol. Metab.* 1983, 57:563-570
- Schleusener H, Joseph K, Mahlstedt J, Kotulla P, Bogner U, Wenzel B, Meinhold.** Differences between immunogenic diffuse toxic goiter (Graves' disease) and goiter with disseminated autonomy: Preliminary results. *J. Mol. Med.* 1980, 4:129-135
- Shong YK, Cho BY, Lee HK, Koh C-S, Min HK, Lee M.** Blocking TSH receptor antibodies incidentally found in transient hypothyroidism during the clinical course of subacute thyroiditis. *J. Kor. Soc. Endocrinol.* (Abstr. 8) 1987a, p62
- Shong YK, Cho BY, Lee HK, Koh C-S, Min HK, Lee M.** TSI measurements using FRTL5 cells in autoimmune thyroid diseases and their clinical significance. *Kor. J. Int. Med.* (Abstr. 39) 1987b, p185
- Shong YK, Cho BY, Lee HK, Koh C-S, Min HK, Lee**

M. Pathogenetic roles of blocking TSH receptor antibodies in primary myxedema-inhibition of bTSH-induced cAMP production in FRTL5 cells. *Kor. J. Int. Med.* (Abstr. 39) 1987c, p186

Strakosch DR, Wenzel BE, Row VV, Volpe R. Immunology of autoimmune thyroid disease. *N. Engl. J. Med.* 1982, 307:1499-1502

Smith BR, Creag FM, Hashim FA, Howells RD, Jones ED, Kajita Y, Buckland PR, Peterson BV. TSH receptor antibodies. *Mount Sinai J. Med.* 1986, 53:53-60

Tamai H, Ohsako N, Takeno K, Fukino O, Takahashi H, Kuma K, Kumagai LF, Nagataki S. Changes in thyroid function in euthyroid subjects with a family history of Graves' disease: A follow-up study of 69 patients. *J. Clin. Endocrinol. Metab.* 1980, 51: 1123-1128

Topliss D, How J, Lewis M, Row VV, Volpe R. Evidence for cell-mediated immunity and specific suppressor T lymphocyte dysfunction in Graves' disease and diabetes mellitus. *J. Clin. Endocrinol. Metab.* 1983, 57:700-705

Valente WA, Yavin Z, Yavin E, Grollman EF, Schneider M, Rotella CM, Zonefrati R, Toccafondi RS, Kohn LD. Monoclonal antibodies to the thyrotropin receptor; the identification of blocking and stimulating antibodies. *J. Endocrinol. Invest.* 1982, 5:293-301

Weiss M, Ingbar SH, Winblad S, Kasper DL. Demonstration of a saturable binding site for thyrotropin in *Yersinia enterocolitica*. *Science* 1983, 219:1331-1333

Wenzel KW, Lente JR. Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against an immunosuppressive action of thionamide drugs. *J. Clin. Endocrinol. Metab.* 1984, 58:62-69

Witebsky E, Rose NR. Studies on organ specificity. IV. Production of rabbit thyroid antibodies in the rabbit. *J. Immunol.* 1956, 76:408-416

=국문초록=

갑상선 질환의 자가면역 병인론

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자가면역성기전이 갑상선질환의 병태생리에 관여한다는 여러가지 증거가 제시되어, 체액성면역과 세포성면역상 자가항원에 대한 관용의 장애와 각 환자의 면역유전학적 배경에 특성이 있음이 이러한 기전에 대한 증거로 생각되고 있다. 체액성면역현상에 있어서 자가면역성 장애의 역할을 규명하기 위하여 갑상선질환환자에서 발견되는 대부분의 자가항체에 대하여 보고된 업적과 저자의 소견을 제시하고 이들 자가항체 각각의 의의를 논의하였다. 특히 TSH수용체항체는 Graves병의 원인물질로 생각되고 있으므로 Graves병에 대한 TSH수용체항체의 병태생리학적이며 임상적인 의의를 저자의 소견을 바탕으로 논의하였으며, 일차성 점액수종환자에서는 TSH수용체항체가 차단항체로 작용한다는 제안에 대한 저자의 소견을 제시하였다. 세포성면역의 장애에 대하여는 갑상선질환의 병인으로서의 세포성면역자체의 역할과 체액성면역장애를 조절하는 역할을 한다는 관점에서 그 기능상의 장애를, 조절면역세포와 갑상선세포의 상호작용에 대한 기능적 장애로서 제시하였다. 이어 갑상선질환에서 관찰되는 면역유전학적 배경의 의의를 논의하였으며, 이들 소견을 종합하여 갑상선질환에 있어서의 자가면역성 병인론의 기전을 제시하였다.