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Mechanisms of Autoimmunity
—Recent concept—

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Abstract: Autoantibodies and autoreactive T cells, which exist even in healthy individuals, are usually regulated by a mechanism called immunological tolerance. For example, peripheral T cells are subject to various types of regulatory mechanisms, including clonal deletion, anergy, clonal ignorance, and T cells with regulatory functions. It is believed that autoimmune response may initiate when such regulated immune responses are pathologically activated by a certain trigger, probably a limited antigenic stimulation. Thereafter, other factors that promote autoimmune responses combine to develop an autoimmune disease. It is estimated that T cells are closely involved in these reactions.

Key words: Immunological tolerance; Molecular mimicry; Epitope spreading

Introduction

Autoimmunity is generally defined as a phenomenon in which antibodies or T cells react with autoantigens. Autoimmunity induces autoimmune diseases. Recent studies have revealed that such autoantibodies or autoreactive T cells exist even in healthy individuals. The immune system has various mechanisms to suppress the immune response to the self, and the disturbance of these mechanisms results in autoimmune diseases.

Autoimmunity and Autoimmune Diseases

The conventional clonal deletion theory assumes that the immune system definitely distinguishes between self and non-self, and that autoreactive B and T cell clones are eliminated before they mature. However, recent studies have demonstrated that this theory, although basically correct, does not always hold true. B and T cells that react with autoantigens exist in the peripheral blood of healthy individuals.

For example, T cells that react with autoantigens, such as myelin basic protein (MBP) of myelin sheath and type II collagen of cartilage, can be separated from the peripheral blood of healthy individuals. Furthermore, autoimmune diseases such as thyroiditis can be induced in normal animals by immunizing them with organ-specific antigens such as thyro-

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globulin, indicating that lymphocytes that react with the autoantigens exist in normal animals. Therefore, it is believed that the existence of autoantibodies or autoreactive T cells is not enough to elicit autoimmune diseases. In addition, it has been recently speculated that auto-reactivity at a low level is physiological and necessary for a normal immune response. It has been reported that the weak reactivity to autoantigens presented by major histocompatibility complexes (MHC; for humans, HLA) might be necessary for the survival of peripheral mature T cells and maintenance of homeostasis.

Considering these factors, it is important to distinguish specific autoimmune responses that cause various autoimmune diseases from the existence of autoreactive lymphocytes or simple autoimmune response. For example, injection of spermatozoa into an animal results only in the production of autoantibodies against spermatozoa, but it does not cause any disease. However, the immunization of an animal with spermatozoa mixed with an adjuvant that strongly stimulates an immune response results in autoimmune testitis. Therefore, autoimmune diseases are distinguished from mere autoimmune response not by the presence/absence of autoimmune response, but by the different quality and quantity of the autoimmune response.

Autoimmune diseases are divided into two groups: the organ-specific autoimmune diseases, in which the target antigens and the tissue disorders are localized in one organ, and the systemic autoimmune diseases, in which the response to a certain type of antigens that are expressed widely in the body, such as an intranuclear antigen and multiple organs are involved. There are several autoimmune diseases that stand between these two groups. It remains unclear whether these two groups of autoimmune diseases result from the same or substantially different mechanisms.

Mechanisms of Immunological Tolerance

Immunological tolerance is defined as a state in which the immune system does not positively respond to autoantigens. The concept of immunological tolerance for autoreactive T and B cells has been changing rapidly as new experimental systems have been established.

T cells, which play a central role in acquired immunity, undergo clonal deletion by apoptosis when they are exposed to a sufficient amount of autoantigens in the thymus where they differentiate. This is called central tolerance. It has been revealed recently that some molecules previously considered to be expressed only in a specific organ are also expressed in medullary epithelial cells of the thymus. This indicates that the thymus is intended to express as many autoantigens as possible in the body to induce tolerance for them. However, this mechanism is limited by the fact that not all autoantigens are expressed in the thymus. Furthermore, T cells that weakly react with autoantigens can migrate into peripheral tissue. Each antigen should have multiple amino acid sequences that can bind to antigen-presenting MHC molecules. These sequences are called epitopes or antigenic determinants. However, some epitopes are not presented as antigens under usual conditions probably due to the relationship with other epitopes or proteolysis in the cells. Such epitopes are called "cryptic epitopes," which means hidden antigenic determinants. T cells cannot become tolerant to them.[1)]

T cells that migrate into peripheral tissues undergo clonal deletion by apoptosis in the similar way as in the thymus when the stimulus of autoantigens is strong. When the stimulus is not strong enough, T cells undergo clonal anergy (clonal paralysis). When the amount of autoantigens is further reduced, T cells become ignorant (non-tolerant and unresponsive). In this regard, it is important that naïve T cells circulate only in lymphoid organs without

entering other organs to maintain the state of ignorant.

It has also been reported that tolerance may be actively suppressed by regulatory T cells. Recent studies have reported T cells with various regulatory functions, including those that produce cytokines with suppressive effects, such as interleukin (IL)-10 and transforming growth factor (TGF)-β, and those that have CD4+ and CD25+ surface markers and provide suppressive effect through cell-cell contact. These various suppressive T cells may play different roles, depending on the activation of autoreactive T cells.

Thus, autoreactive T cells are under substantially different conditions of tolerance, depending on the quality and quantity of autoantigens. For example, many autoantigens are too isolated from the immune system to activate potential autoreactive T cells. Autoantigens expressed on non-hematopoietic cells may not stimulate T cells because they do not have co-stimulatory molecules. Another mechanism has also been revealed in which the lymph nodes around organs have dendritic cells that take antigens to induce tolerance of autoreactive T cells in the steady state condition.

B cells have been reported to undergo anergy in response to soluble autoantigens and clonal deletion in response to stronger autoantigens, such as those on cell surfaces in the bone marrow where they differentiate. B cells that strongly react with soluble antigens such as self-molecules at the germinal center of peripheral tissues are also deleted through apoptosis. B cells have been reported to cause a phenomenon called receptor editing in which B cells that react with an autoantigen rearrange the gene of the antigen receptor (immunoglobulin) once again to make another non-autoreactive receptor.

Mechanism of Initiation of Autoimmunity

It is generally believed that autoimmunity is triggered by the development or activation of CD4+ helper T cells that react with a specific autoantigen. Based on various evidence, it is now proposed that a specific antigenic stimulus is the first trigger of autoimmunity. This is called the "single initiating antigen hypothesis".[2] For example, molecular mimicry in which immune response occurs to both an external microbial antigen and an autoantigen because of their homology is considered one of the mechanisms of initiating autoimmunity.

Microbial infection may initiate autoimmune response not only through molecular mimicry, but also with polyclonal activation and release of isolated autoantigen. Lipopolysaccharide (LPS), a product of infectious microbes, bacterial DNA, and viruses serve as an adjuvant to immune response. They bind to Toll-like receptors (TLRs) on the surface of macrophages or dendritic cells to stimulate natural immunity and inflammatory cytokine production, enhancing immune response by increasing the expression of MHC antigen or co-stimulatory molecules, such as B7-2 and OX40L. These responses are usually helpful for inducing acquired immunity, but may stimulate potential autoreactive T cells. Through these processes, it is also possible that cryptic epitopes not expressed under usual conditions are expressed to trigger an autoimmune response.

Non-infectious factors are also considered as a trigger of autoimmunity. For example, estrogen exacerbates systemic lupus erythematosus (SLE) in a mouse model, while drugs, such as procaine amide and hydralazine, induce the production of antinuclear antibodies, causing an SLE-like pathologic state. The amount of iodine intake is an important environmental factor in autoimmune thyroid disease.

Mechanisms of Development of Autoimmune Diseases

Triggering autoimmunity alone probably results in a transient event and is insufficient to induce autoimmune disease. Studies in mouse

models have shown that CD4+ T cells may be required to complete the pathological state of most autoimmune diseases. Animal experiments have demonstrated that the onset of autoimmune diseases can be suppressed by removing or inhibiting the function of CD4 cells with anti-CD4 monoclonal antibodies. Furthermore, the importance of antigen-specific CD4 cells in pathological autoimmune condition has been suggested from the association with MHC class II antigens (such as DR antigen of HLA in humans), infiltration of CD4+ cells in many organ-specific autoimmune diseases, and production of autoantibodies of IgG type.

Although various factors are associated with the progression of autoimmune diseases, one of the important phenomena is epitope spreading. Epitope spreading refers to a phenomenon in which autoantigens (antigen determinants) detected by T and B cells increase during the process from the initial activation of autoreactive lymphocytes to the chronic phase. This concept is important for explaining, for example, the mechanism by which autoimmune response induced by one cryptic epitope leads to complete autoimmune response. Both B and T cells are involved in this phenomenon. Particularly, B cells play an important role as antigen-presenting cells for T cells.

In contrast, a study using non-obese diabetic (NOD) mice as a type I diabetes model showed that autoimmune disease may progress through the avidity maturation and selective expansion of a particular antigen-specific T cell clone. We have also shown from the analyses of T cell clonality infiltrating into organs that reactive epitope is not always spread during the progress of a disease. Probably, such positive and negative balance of immune responses with regard to reactive epitopes may be involved in the persistence and progression of autoimmune diseases.

Conclusions

Autoimmune disease is generated through the disturbance of immunological tolerance. Activation of autoreactive lymphocytes, and various positive and negative immune responses are involved in each of these processes. Genetically, individuals with lower threshold to these responses are more susceptible to autoimmune disease, although various environmental factors that induce such immune responses are also significant. It is thus necessary to understand in detail autoimmune phenomena in each patient to establish a proper therapy that suppress pathological immune responses without affecting normal immune functions.

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Fundamentals of Treatment for Autoimmune Diseases

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Abstract: Autoimmune diseases are dichotomized into organ-specific and systemic one. Hashimoto's disease, Addison's disease, and pernicious anemia are the representatives of the former and systemic lupus erythematosus of the latter. Systemic disease is treated mainly by rheumatologists and organ-specific disease is in the hands of the specialists to the organs involved. Autoantigens specific to the organs involved are targeted in organ-specific disease, and, nuclei without organ-specificity are the main targets in systemic disease. Although more concrete evidence of autoimmune phenomena for their pathogenesis is obtained in organs-specific disease than systemic disease, immunosuppression by glucocorticoids and immunosuppressants is applied only to the latter. It is very difficult to determine the amount of glucocorticoids least but sufficient to suppress the disease, and, it is sometimes based upon the doctors' experience. This is why it is called "art instead of science" how to use glucocorticoids. On the other hand, hormone replacement therapy is the treatment-rule for organ-specific disease instead of immunosuppression and it might be even forgotten that autoimmune process underlies there. These two categories of autoimmune disease are in striking contrast in terms of both pathogenesis and treatment.

Key words: Systemic autoimmune disease; Organ-specific autoimmune disease; Glucocorticoid; Immunosuppressive agent; Pernicious anemia

Introduction

Autoimmune diseases are roughly divided into two categories: systemic and organ-specific. The former is a group of diseases, which is called collagen-vascular diseases more popularly. Organ-specific autoimmune disease is the one usually not in hands of rheumatologists but in those of the specialists for the organs involved, such as endocrinologists, neurologists, gastroenterologists, and so on.

There are two interesting features between the

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two groups. First, organ-specific autoimmune diseases have more concrete evidence for the involvement of autoimmune processes than systemic ones, such as the evidence for existence of autoantigen-specific T lymphocytes.[1)] Secondly, in spite of this, immunosuppression by glucocorticoids or immunosuppressive agents is applied to only systemic autoimmune diseases and almost never to organ-specific ones. As a matter of fact, it is sometimes forgotten that organ-specific autoimmune diseases have autoimmune mechanisms underlain for the pathogenesis.

These aspects are easier to understand when we review the characteristics of the two groups of autoimmune diseases.

Characteristics of Systemic Autoimmune Diseases (Organ-Nonspecific Autoimmune Diseases, So-Called Collagen Vascular Diseases)

Let's look at the disease character of systemic lupus erythematosus (SLE) as a representative of systemic autoimmune diseases. It is well-known that patients with SLE have anti-nuclear antibodies in their circulation as the most paramount feature. Every nucleated cell in the body has a nucleus inside, and there is no organ-specificity in this regard. Anti-nuclear antibodies interact with nuclei and elicit inflammation by consuming complements when nucleated cells are destroyed and release the nuclear materials in the circulation or in the tissue fluids.

Kidney is the organ targeted most frequently in SLE and the resultant glomerulonephritis is called "lupus nephritis". Sixty to seventy percent of the patients with SLE develop lupus nephritis, although autoantibodies strictly specific to glomeruli are scarcely seen. As mentioned above, lupus nephritis develops as a result of immune complexes formed in the circulation or *in situ*, which eventually accumulate in glomeruli.

There are three major anatomical characteristics of the kidney in this regard. First, kidneys receive ~25% of the blood that is pumped up by the heart every minute. That is, they receive ~50 times more blood than other organs in the body based upon weight by weight. Therefore, the kidney is an organ quite rich in blood flow. Second, glomerular vascular structure is composed of afferent arterioles, glomerular capillaries, and efferent arterioles. As a matter of fact, glomerular capillaries are sandwiched by the arterioles. Probably due to this anatomical characteristic, pressure in the glomerular capillary is ~4 times higher than the one in the capillaries elsewhere. Thirdly, the kidney is an apparatus for filtering body fluid and it makes ~150 l/day of glomerular filtration. Immune complexes could passively be deposited in the glomeruli from patients with SLE as a result of these anatomical and physiological characteristics.

There are many reports indicating that anti-dsDNA antibodies, in particular, have strong glomerulonephritogenic activities. Thus, treatment modality has been developed to eliminate B cells specific for anti-dsDNA antibodies, although it is not widely prevailed. A part of anti-dsDNA antibodies might indeed more preferentially be deposited in the glomeruli than autoantibodies specific for other autoantigens, it is quite difficult to ascribe lupus nephritis to only one autoantigen-autoantibody system. Because anti-dsDNA antibodies are highly specific to SLE and reflect the disease activities in most cases, lots of autoantibodies, in terms of both quality and quantity, specific to many cell components are produced by the time anti-dsDNA antibodies emerge and, consequently, higher amount of immune complexes are deposited in the glomeruli.

Because T lymphocytes are indispensable for antigen-specific antibody formation, it is widely believed that they play a pivotal role also in autoantibody production in SLE. However, one of the most perplexing things in systemic autoimmune diseases is the difficulty in show-

ing the existence of such T lymphocytes in SLE.[2] We are only speculating indirectly the presence of such T lymphocytes by analyzing the molecular characteristics of autoantibodies including anti-nuclear antibodies.[3] Questions remain to be answered as to autoantigen which initiates the autoimmune process.

Fundamentals for the Treatment of Systemic Autoimmune Diseases

Because of the reasons mentioned above, it is impossible, at this moment, to utilize autoantigens or a part of an autoantigen to eliminate pathogenic and antigen-specific T or B lymphocytes. Therefore, overall immunosuppression is needed to achieve sizable effects in the treatment of systemic autoimmune diseases.

1. Glucocorticoids (Corticosteroids)

After all, glucocorticoids are most frequently used for the treatment of systemic autoimmune diseases. How to use glucocorticoids in treating autoimmune disease is largely based upon one's experience and this is why it is called "art instead of science" to use glucocorticoids. They have both anti-inflammatory and immunosuppressive effects. For example, prednisolone less than 30 mg/day exerts mainly anti-inflammatory activity, while immunosuppressive effects seem to appear when it is used at the dose of more than 50 mg/day. Glucocorticoids show their effects by binding to the receptor located in the cytoplasm and, after migrating to the nucleus, the complexes bind to the specific sites of the glucocorticoid-responding genes with the resultant protein production.[4]

However, anti-inflammatory effects would be brought about not by inducing glucocorticoid-inducible proteins but by the mechanisms that follow. Transcription factors such as AP-1 and NF-κB are required in order for cells to produce inflammation-inducing proteins that would be released into their microenvironment. The transcription factors accelerate enormously the transcription rate of the inflammatory proteins by binding to the upstream of those genes. Complex molecules composed of glucocorticoids and their receptors bind directly to AP-1 and NF-κB in the nucleus and block the latter molecules to bind their specific transcription sites, thereby inhibiting the production of inflammation-inducing proteins.

On the other hand, immunosuppressive effects of glucocorticoids would be due to the alteration qualitatively and quantitatively in the function of T lymphocytes and antigen presenting cells. Thus, prednisolone less than 30 mg/day is used when anti-inflammatory effects are pursued and more than 50~60 mg/day of prednisolone are needed to achieve immunosuppressive effects. There are big variations among artificial glucocorticoids in their half-lives when given *in vivo*, and we need to understand that the longer the half-lives, the more potent in both their beneficial and deleterious effects. Glucocorticoids show anti-inflammatory effects very swiftly, while immunosuppression is a late effect.

2. Immunosuppressive agents

A group of drugs classified as immunosuppressive agents is usually used as an adjunct to glucocorticoids instead of being used solely. They are slow-acting compared to glucocorticoids. Azathioprine and cyclophosphamide are more frequently used than cyclosporine A and FK506 in Japan. However, the latter two are required to suppress T-lymphocyte function more specifically. Cyclophosphamide is used either *per os* every day or intravenously as a pulse-therapy once a month. The latter is believed to be less toxic with almost equal beneficial effects.[5]

Outline of Organ-Specific Autoimmune Diseases and Fundamentals of the Therapy Thereof

Organ-specific autoimmune diseases are dichotomized from the therapeutic point of view. Hashimoto disease, Addison disease, pernicious

anemia, and type I diabetes mellitus comprise one side and the other side includes multiple sclerosis for example.

Let's look at the pernicious anemia caused by deficiencies of vitamin B_{12} or folic acid. Vitamin B_{12} needs to couple to the intrinsic factor, which is released from the parietal cell of the stomach, to be absorbed via the specific receptor located in the ileum. There are two kinds of autoantibody found in pernicious anemia: the one which inhibits the binding of vitamin B_{12} to the intrinsic factor[6] and the other which blocks the binding of vitamin B_{12}-intrinsic factor complex to the receptor in ileum.[7] Production of intrinsic factor is decreased in atrophic gastritis, where antibody- and cell-mediated autoimmune mechanisms are operative in destroying parietal cells in the stomach.

Although pernicious anemia is induced by an autoimmune mechanism, its specific therapy is intramuscular injection of vitamin B_{12}. Glucocorticoids or immunosuppressants are never used to suppress the autoimmunity which underlies pernicious anemia. This principle holds true in Hashimoto's disease, Addison's disease, and type I diabetes mellitus. Replacement therapy with thyroid hormone and insulin is applied to Hashimoto's disease and type I diabetes, respectively. Although glucocorticoids are indeed used for treatment of Addison's disease, this is not for suppression of autoimmune mechanism but for the replacement of the adrenal hormone. Therefore, glucocorticoids in high amount are never used in Addison's disease. Even if the function of these endocrine organs is destroyed completely through autoimmune mechanism, replacement therapy with the corresponding hormone is possible and much safer than aggressive immunosuppressive therapy.

The situation is quite different in multiple sclerosis and replacement therapy is not applicable here. Autoimmune process *per se* must be stopped to improve central nervous system function and we need to resort to glucocorticoids in high dose or immunosuppressants just like in systemic autoimmune diseases.

Number of autoantigens eliciting autoimmune process is fewer in organ-specific autoimmune diseases than in systemic autoimmune diseases and the identification of their molecular nature is rapidly progressing. We hope, in the near future, to suppress autoimmune process by the specific autoantigens or the epitopes thereof.

Conclusion

Most organ-specific autoimmune diseases are treated by endocrinologists and the replacement of hormone is the treatment principle. It is sometimes forgotten that autoimmune mechanisms are operative in these organ-specific autoimmune diseases.

On the other hand, many organs are involved in systemic autoimmune diseases and the introduction of high dose glucocorticoids or immunosuppressants is the treatment rule. Glucocorticoids also have adverse effects systemically and it is quite important to use the smallest amount required to suppress disease processes. However, this is very difficult to achieve and it is often referred to as "art rather than science" to decide the amount of glucocorticoids to be used. It might be a trick to start treatment with enough amount of glucocorticoids and to taper as swiftly as possible. We need to be alert to opportunistic infections around 4 weeks from the initiation of the treatment and prophylactic measures should be taken by checking and referring to the number of total lymphocytes or $CD4^+$ T lymphocytes.

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Autoimmune Hematological Diseases

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Abstract: Idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), and pernicious anemia are autoimmune hematological diseases associated with autoantibodies against platelets, red blood cells, and gastric mural cells and intrinsic factor, respectively. The diagnosis of ITP requires thrombocytopenia with normal morphology of red blood cells and white blood cells (except for cases complicated with AIHA or iron-deficiency anemia). Bone marrow examination indicates a normal or increased number of megakaryocytes. The first-line treatment is the administration of glucocorticoids, and splenectomy is performed in patients who are unresponsive to initial glucocorticoid therapy. The diagnosis of AIHA requires findings indicating hemolysis and serological evidence of anti-red blood cell (RBC) autoantibodies. Like ITP, the first-line treatment is the administration of glucocorticoids. Splenectomy and the administration of immunosuppressive agents are considered in patients who are unresponsive to initial glucocorticoid therapy. Neurological symptoms in addition to anemic symptoms are common in patients with pernicious anemia. The diagnosis of pernicious anemia requires findings of dyserythropoiesis and low vitamin B_{12} value. Anti-intrinsic factor and/or anti-gastric mural cell antibodies are often positive. Pernicious anemia is treated with the intramuscular injection of vitamin B_{12}.

Key words: Idiopathic thrombocytopenic purpura;
Autoimmune hemolytic anemia; Pernicious anemia

Introduction

Idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), and pernicious anemia are autoimmune hematological diseases associated with autoantibodies against platelets, RBCs, and gastric mural cells and intrinsic factor, respectively.

This paper discusses these three diseases.

Idiopathic Thrombocytopenic Purpura (ITP)

ITP is one of the hematological diseases associated with thrombocytopenia. ITP is an autoimmune thrombocytopenic disorder in

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Table 1 Diagnostic Criteria of Idiopathic Thrombocytopenic Purpura (ITP)
(Investigation and research group of disease specified by the Ministry of Health and Welfare; revised in 1990)

1. Bleeding symptoms are observed.
   The main bleeding symptom is purpura (petechia and ecchymosis), and other symptoms include stomatorrhagia, rhinorrhagia, melena, hematuria, and hypermenorrhea. Usually, no intrajoint bleeding is observed. ITP may be detected in asymptomatic patients found to have thrombocytopenia at a medical checkup.
2. The following laboratory findings are observed.
   1) Peripheral blood
      (1) Thrombocytopenia with platelet count of 100,000/μl or less. Attention should be paid to the possibility of pseudothrombocytopenia when the result is obtained with an automatic hemocytometer.
      (2) Erythrocytes and leucocytes are quantitatively and morphologically normal. Blood loss-induced or iron-deficiency anemia is sometimes observed. A slight fluctuation of leukocyte count may be observed.
   2) Bone marrow
      (1) Megakaryocyte count in the bone marrow is normal or increased. Many of megakaryocytes are lacking in platelet adhesion.
      (2) The cellularity and the morphology of both the erythroid and myeloid series are normal. The myeloid/erythroid ratio (M/E ratio) is normal.
      (3) Platelet-associated immunoglobulin G (PAIgG) is increased.
      The increase in PAIgG is sometimes not observed, while it can be observed in thrombocytopenia associated with other diseases.
3. Other diseases associated with thrombocytopenia can be excluded.[Note)]
4. Idiopathic thrombocytopenic purpura may be diagnosed when a patient meets the above characteristics of (1) and (2) and the above requirement of (3). The shortage of platelet life may be helpful to exclude ITP.
5. Disease type differentiation criteria
   1) Acute type: ITP resolved in 6 months of the estimated onset or diagnosis
   2) Chronic type: ITP that persist for more than 6 months of the estimated onset or diagnosis.
   However, ITP may be considered as the acute type in infants when it develops acutely with prior viral infection.

Note: Diseases that can cause thrombocytopenia include drug or radiation disorder, aplastic anemia, myelodysplastic syndrome, paroxysmal nocturnal hemoglobinuria, systemic lupus erythematosus, leukemia, malignant lymphoma, bone marrow metastasis of cancer, disseminated intravascular coagulation syndrome, thrombotic thrombocytopenic purpura, hypersplenism, megaloblastic anemia, sepsis, tuberculosis, sarcoidosis, and hemangioma. For infection, thrombocytopenia after viral infection or viral live vaccine inoculation in infants may be included in ITP. Congenital types of thrombocytopenia include Bernard-Soulier syndrome, Wiskott-Aldrich syndrome, May-Hegglin syndrome, and Kasabach-Merritt syndrome.

(Kuramoto, A. *et al.*: 1990 Research Report of Specific Disease Specific Organopathy Investigation and Research Group of Ministry of Health and Welfare. 1991; pp. 59–61)

which antiplatelet antibodies bind to platelets and cause accelerated platelet destruction by the reticuloendothelial system, including the spleen. ITP is often diagnosed in patients who visit a clinic with a complaint of bleeding tendency, such as purpura, or who visit a clinic because thrombocytopenia were found at routine medical checkups.

1. Diagnosis of ITP

Patients with ITP often show subcutaneous or submucosal bleeding, although the severity of bleeding symptoms varies. Intrajoint or intramuscle hematomas, as observed in diseases associated with coagulopathy, are rarely observed. ITP patients who are found to have thrombocytopenia at routine medical checkups are often asymptomatic.

Peripheral blood cell count and morphological examination of blood cells should first be performed to diagnose ITP. It is also necessary to exclude pseudothrombocytopenia. Pseudothrombocytopenia occurs when platelet count with an automatic hemocytometer mistakenly reads a low value due to platelet agglutination in a test tube containing ethylenediaminetetraacetic acid (EDTA), an anticoagulant. Pseudothrombocytopenia is reported to occur in about 0.1% of adults and should be suspected in patients with a low platelet value

without clinical symptoms, including bleeding tendency. In such cases, platelet count should be verified to eliminate the possibility of pseudothrombocytopenia by (1) visually checking peripheral blood smear specimens and (2) collecting blood with other anticoagulants such as citric acid and heparin.

Peripheral blood smears from typical ITP patients show thrombocytopenia and normal or slightly larger platelets, with no giant platelets being observed. Erythrocytes and leucocytes are morphologically normal.

When ITP is suspected from peripheral blood smears, further examinations should be performed. According to American Society of Hematology guidelines, suspected patients of less than 60 years of age can be diagnosed as ITP without bone marrow examination, unless findings inconsistent with ITP are observed in medical history, physical examinations, and peripheral blood count or morphology.[1)]

In Japan, however, bone marrow examination is usually performed to verify the normal or increased number of megakaryocytes and to confirm that erythroid and myeloid cells are quantitatively and morphologically normal according to the diagnostic criteria proposed by a research group of the former Ministry of Health and Welfare (currently, the Ministry of Health, Labour, and Welfare), as shown in Table 1. Further examinations may be performed as required for differentiating ITP from other possible diseases listed in the Note of Table 1.[2)]

2. Treatment of ITP

Treatment is not always necessary in patients diagnosed as having ITP. The need for treatment depends on platelet count and severity of bleeding tendency. Although no definite criteria have been established for the indication for treatment, asymptomatic patients or patients with mild purpura who have a platelet count of 50,000/μl or higher at the first presentation are often followed without specific treatment.

In contrast, treatment is necessary for patients with a platelet count less than 20,000/μl, irrespective of symptoms, or those with evident submucosal bleeding and a platelet count less than 50,000/μl. The need for treatment in patients with mild bleeding tendency and a platelet count between 20,000 and 50,000/μl is often examined on a case-by-case basis in consideration of other hemorrhagic risk factors, such as blood pressure and peptic ulcer.

Patients with fatal hemorrhage irrespective of platelet counts, or those with evident submucosal hemorrhage and a platelet count less than 20,000/μl have to be immediately hospitalized for treatment.

The following treatments are available for ITP.

(1) Standard treatment

(i) **Glucocorticoids**: Glucocorticoids are the first-line therapy for ITP. Usually, oral predonisolone (PSL) is used. It is started at 1 mg/kg/day and continued for at least 3 to 6 weeks. Subsequently, the dose is gradually reduced, depending on its effect.

(ii) **Splenectomy**: Splenectomy is indicated in patients who do not respond to glucocorticoids or those who require 0.1 mg/kg/day or higher of PSL to maintain a safe platelet count. Previous reports showed that platelet count returned to normal levels in 60–70% of patients who received a splenectomy.

(2) Emergency treatment

(i) **Immunoglobulin**: Earlier studies reported that administration of an intact type of immunoglobulin at 0.4 g/kg/day for 5 days increased platelets in about 75% of patients with ITP. However, this is usually a transient increase, and the platelet count often returns to the previous level in 3 to 4 weeks.

The administration of immunoglobulin is indicated in patients with a platelet count less than 50,000/μl and fatal hemorrhage, or those who require a transient increase of platelets for surgery.

(ii) **Platelet transfusion**: Platelet transfusion is performed as an emergency measure for patients complicated with fatal hemorrhage.

Table 2 Diagnostic Criteria of Autoimmune Hemolytic Anemia (AIHA)
(Investigation and research group of disease specified by the Ministry of Health and Welfare; revised in 1990)

1. The diagnostic criteria of hemolytic anemia are met.
2. The direct Coombs' test using wide spectrum antiserum is positive.
3. Alloimmune hemolytic anemia (incompatible blood transfusion and hemolytic disease of the newborn) and drug-induced immune hemolytic anemia are excluded.
4. A diagnosis of AIHA is made with the above 3 criteria. AIHA is then further classified into the following 3 disease types by the optimal temperature for the reaction of anti-erythrocyte autoantibodies.
   (1) Warm AIHA
   Warm AIHA clinically varies among patients. In principle, IgG alone, or the combination of IgG and a complement factor is detected in the direct Coombs' test at 37°C using specific antiserum. However, there may be cases positive only for anti-complement or wide spectrum antiserum. This type of AIHA may be diagnosed by excluding the following (2) and (3).
   (2) Cold agglutinin syndrome (CAS)
   Serum cold agglutinin is increased, and exacerbated hemolysis by the exposure to cold or chronic hemolysis is observed. Complement components are detected at the direct Coombs' test at 4°C.
   (3) Paroxysmal cold hemoglobinuria
   Hemoglobinuria and detection of serum biphasic hemolysin (Donath-Landsteiner antibody) characterize this disease.
5. The clinical course and cause of AIHA are classified as follows:
   Acute type: Resolved within 6 months of the estimated onset or diagnosis.
   Chronic type: Persisted for more than 6 months of the estimated onset or diagnosis.
   Idiopathic type: No underlying disease is observed.
   Secondary: A prior or concomitant underlying disease is observed.
6. Remarks
   1) Morphological findings of erythrocytes (spherocytes and hemagglutination) are helpful for making a diagnosis of AIHA.
   2) Occasionally, the direct Coombs' test by the common method is negative in some cases with warm AIHA.
   3) Idiopathic warm AIHA may be complicated with idiopathic thrombocytopenic purpura (ITP).
   4) Hemolysis of cold agglutinin syndrome does not always occur in parallel with cold agglutinin titer: hemolytic symptoms may occur even at a low titer.
   5) Antibody emigration technique is used to determine the properties of autoantibodies. Further examination may be performed, as required, because some autoantibodies may show special properties, depending on the type of immunoglobulin and immunobiological activity.
   6) Underlying diseases include autoimmune diseases, rheumatic diseases, lymphoproliferative disorders, immunodeficiency syndrome, tumors, and infections (mycoplasma and virus). These diseases may become evident during the clinical course of patients with idiopathic AIHA. AIHA associated with prior viral infection in infants shall be considered idiopathic. Cold agglutinin syndrome associated with mycoplasma or viral infection shall be considered secondary.
   7) Attention should be paid to the fact that the direct Coombs' test with wide spectrum antiserum is positive in drug-induced immune hemolytic anemia. It is helpful for making a diagnosis of the drug-induced anemia to examine the clinical course and effect of the discontinuation of the potentially responsible drug. Except for the autoimmune type (α-methyldopa), drug specificity of antibodies can be proved with appropriate techniques. For the autoimmune type, the direct Coombs' test may become positive after the long-term administration of the responsible drug, and warm AIHA may occur in some patients.

(Maekawa, T.: Research Report of Diseases Specified by the Ministry of Health and Welfare: Idiopathic Hematopoietic Disorder. 1991; pp. 64–70)

However, the effect is temporary because antiplatelet antibodies bind to transfused platelets and cause platelet destruction.

(3) Treatment for intractable cases

(i) **Immunosuppressive agents**: Immunosuppressive agents (cyclophosphamide, azathioprine and cyclosporine) have been administered in patients with refractory ITP. Vincristine and danazol are also used. However, their effect is variable.

(ii) ***H. pylori* eradication therapy**: Recent clinical trials in ITP patients positive for *Helicobacter pylori* reported that platelet counts increased after *H. pylori* eradication therapy.[3–5] Although it remains unclear how *H. pylori* is involved in the onset of ITP, the therapy deserves further investigation.

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) develops because anti-RBC autoantibodies (IgC or IgM) bind to RBCs and cause accelerated RBC destruction by the reticuloendothelial system, including the spleen. AIHA is classified by the characteristics of autoantibodies into warm AIHA, which has warm-type IgG antibodies, cold agglutinin syndrome (CAS), which has cold-type IgM antibodies, and paroxysmal cold hemoglobinuria (PCH), which has biphasic IgG antibodies (Donath-Landsteiner (D-L) antibodies).

1. Diagnosis of AIHA

Patients with AIHA often complain of anemic symptoms, including palpitations and dypnea on exertion, although their severity differs by patient. Physical examination of the AIHA patient reveals anemia, jaundice, and splenomegaly. To make a diagnosis of AIHA, it is necessary to (1) detect clinical or laboratory finding(s) suspected to indicate hemolysis, and (2) serologically demonstrate anti-RBC antibodies. The diagnostic criteria of the research group of the former Ministry of Health and Welfare (currently the Ministry of Health, Labour, and Welfare), revised in 1990,[6] are used in Japan. See Table 2.

Laboratory findings suggesting hemolysis include anemia, increased reticulocytes, increased bilirubin with the predominant increase of indirect bilirubin, increased LDH, and reduced haptoglobin. Anti-RBC antibodies can be demonstrated by detecting immunoglobulins or complement components combined with RBC membrane using direct Coombs' test.

When the direct Coombs' test is negative in patients with typical AIHA findings, it is necessary to quantitatively determine immunoglobulin combined with RBCs. It is also necessary to perform the direct Coombs' test at different temperatures because AIHA is classified into subtypes by the temperature at which antibodies become active.

AIHA is classified into warm AIHA when antibodies (IgG) become active around 37°C; into CAS when cold-type IgM antibodies show strong activity at as low as 0 to 4°C with almost no activity at physiological temperature; and into PCH when D-L antibodies (IgG) that bind to RBC at 0 to 4°C and dissociate from RBC at 37°C. However, prior to dissociation, D-L antibodies initiate complement activation and cause homolysis.

It is important to ask patients about their medical history because AIHA may develop in patients with an underlying disease (systemic lupus erythematosus, malignant lymphoma, or chronic lymphocytic leukemia) or infection (such as mycoplasma) or those who are taking drugs (such as α-methyldopa).

2. Treatment for AIHA

(1) Treatment for warm-type AIHA

Usually, folic acid is administered to increase hematopoiesis. The need for further treatment depends on the severity of hemolysis. The first-line therapy is the administration of glucocorticoids: usually 1 mg/kg/day of oral PSL is administered. Hemolysis is usually ameliorated within 3 weeks, and PSL is gradually reduced after 4 to 6 weeks of treatment. Although PSL can be discontinued in some patients, a maintenance dose of 10 to 15 mg/day is often required. Splenectomy and/or administration of an immunosuppressive agent is performed on patients who do not respond to PSL or those who require a high dose of PSL to maintain RBCs, as in the treatment for ITP.

(2) Treatment for CAS

CAS develops both primarily and secondarily. Primary CAS is often associated with mild anemia, and is therefore treated merely by instructing patients to avoid cold stimuli. Severe patients may be treated with an immunosuppressive agent or plasmapheresis, while the administration of glucocorticoids or splenectomy are not so effective. Patients with secondary CAS associated with advanced

hemolysis require the treatment of their underlying diseases.

(3) Treatment for PCH

Usually, PCH does not require any specific treatment except for avoiding cold stimuli. However, plasmapheresis is indicated in serious cases with fatal risk. Underlying syphilis should be suspected in patients with chronic PCH.

Pernicious Anemia

Pernicious anemia results from vitamin B_{12} deficiency. Although vitamin B_{12} deficiency can occur from insufficient intake, gastrectomy, or small intestine disease, only the anemia associated with vitamin B_{12} deficiency by chronic atrophic gastritis is called pernicious anemia.

1. Diagnosis of pernicious anemia

Pernicious anemia develops and progresses slowly. The diagnosis of pernicious anemia is often made in patients around 60 years of age. In addition to anemic symptoms, this disease is associated with neurological symptoms (abnormal sense of perception, vibration, and position as well as positive Romberg's sign, reduced muscle strength, and spastic gait) and lingual papilla atrophy (Hunter's glossitis). Peripheral blood testing indicates macrocytic anemia and hypersegmented neutrophils often associated with leukopenia and thrombocytopenia.

Since hematopoiesis is ineffective, biochemical tests show increased LDH, increased indirect bilirubin, and reduced haptoglobin. Vitamin B_{12} is low. The diagnosis of pernicious anemia can be confirmed in the Schilling test indicating that the absorption of vitamin B_{12} is low and recovered with the addition of the gastric intrinsic factor.

Furthermore, patients with pernicious anemia show immunological abnormalities, such as the development of anti-intrinsic factor antibody (highly specific because it is positive in about 70% of patients) and anti-gastric mural cell antibody (positive in about 90% of patients).

Bone marrow examination indicates megaloblastic cells, giant metamyelocytes, and giant rod nuclear cells, although diagnostic bone marrow examination is not necessarily required in typical cases.

2. Treatment for pernicious anemia

The first-line therapy for pernicious anemia is the intramuscular injection of vitamin B_{12}: usually, 1,000μg/day of hydroxocobalamin or methylcobalamin is administered for about 2 weeks continuously, which improves anemia and replaces a sufficient amount of vitamin B_{12}. Subsequently, maintenance therapy is necessary every 2 to 3 months. An earlier study reported that there is another vitamin B_{12} absorption route that does not require the gastric intrinsic factor, and that the oral administration at 2,000μg every day was comparable to, or more effective than, the intramuscular injection of 1,000μg once a month.[7)]

Conclusion

This paper explains the latest view of the diagnosis and treatment of ITP, AIHA, and pernicious anemia. We hope that this paper will be helpful for those who encounter clinical cases suspected to have the diseases.

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Autoimmune Endocrine Diseases

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Abstract: Autoimmune endocrine diseases occur most frequently among various autoimmune diseases. Among autoimmune endocrine diseases, Graves' disease, Hashimoto's disease, type 1 diabetes mellitus, and Addison's disease are especially frequent in daily clinical practice. Graves' disease produces thyrotoxicosis due to the effects of the anti-TSH receptor antibody upon the thyroid gland and diverse symptoms due to its effects on extrathyroid tissues. Hashimoto's disease is the most frequently encountered autoimmune disorder, and cellular immunity is thought to be involved. Guidelines for the diagnosis of these thyroid diseases have been provided by the Japan Thyroid Association. Autoimmune mechanisms are involved in many cases of type 1 diabetes mellitus. Type 1 diabetes mellitus has a wide spectrum of clinical disease states ranging from the rapid onset form, which develops diabetes mellitus within several days, to SPIDDM, which slowly progresses over years. Addison's disease is also an autoimmune disorder in many cases and may present polyglandular autoimmune syndrome with complications by other organ-specific autoimmune disorders.

Key words: Graves' disease; Hashimoto's disease; Type 1 diabetes mellitus; Addison's disease

Introduction

It is generally recognized that endocrine organs may contract various organ-specific autoimmune diseases, which, except for Basedow's disease (Graves' disease) in which autoantibodies possess endocrine gland-stimulating activity, present diverse clinical features due to endocrine hypofunction through autoimmune mechanisms. Widely known among these disorders is polyglandular autoimmune syndrome involving autoimmune endocrine diseases of several organs.

This paper presents brief accounts of Graves' disease, Hashimoto's disease, type 1 diabetes mellitus, and Addison's disease, which are frequently seen autoimmune endocrine diseases in daily clinical practice.

Graves' Disease

1. Pathophysiology

The disease is characterized by the presence of an autoantibody that recognizes the TSH

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receptor and stimulates the thyroid gland (i.e., anti-TSH receptor antibody), goiter, and signs of thyrotoxicosis. Exophthalmos and pretibial myxedema, which are also characteristic features of Graves' disease, cannot be explained by excess thyroid hormones and currently are considered to be ascribable to the reactions of antibody to TSH receptors in adipocytes, etc.[1)]

2. Clinical features and physical findings

Merseburg's triad (palpitations, struma, and exophthalmos) is important as symptoms and findings in Graves' disease. Other major symptoms include weight loss (with an associated increase in appetite), fatiguability, shortness of breath, hyperidrosis, finger tremors, diarrhea, periodic paralysis (male), and muscle weakness.

Physical findings include (1) diffuse struma (vascular murmurs audible); (2) ocular symptoms exophthalmos, lid lag and Graefe's sign; (3) tachycardia and atrial fibrillation; (4) warm moist skin; (5) tremors; and (6) pretibial myxedema.

3. Laboratory findings

(1) **Routine examination**: Elevation in serum ALP (bone type isozyme), a slight increase in AST/ALT, low serum cholesterol level, and a slight increase in blood glucose are noted.

(2) **Endocrine tests**: Low serum TSH level and elevations in free T_3 and free T_4 in serum are observed. Patients show elevated radioactive iodine uptake (30% or more).

(3) **Immunological tests**: Patients are positive for anti-TSH receptor antibody. For serum anti-TSH receptor antibody determination, two different assay methods are currently available: 1) measurement of the degree of inhibition of binding to labeled TSH receptor (TBII, TRAb) and 2) measurement of cAMP production in cultured thyroid cells (TSAb). Usually, one or the other of the tests is performed first, and if the test is found negative, then the other test is undertaken.

(4) **Imaging diagnosis**: Ultrasonographic examination reveals diffuse enlargement of the thyroid with low internal echo level. Enhanced internal blood flow is noted on Doppler ultrasonography.

Table 1 Guidelines for the Diagnosis of Graves' Disease

a) Clinical findings
   1. Signs of thyrotoxicosis such as tachycardia, weight loss, finger tremor, and sweating
   2. Diffuse enlargement of the thyroid gland
   3. Exophthalmos and/or specific ophthalmopathy

b) Laboratory findings
   1. Elevation in serum free thyroxine (FT_4) level
   2. Suppression of serum thyroid stimulating hormone (TSH): less than $0.1\mu U/ml$
   3. Positive for anti-TSH receptor antibody (TRAb or TBII) or thyroid stimulating antibody (TSAb)
   4. Elevated radioactive iodine (or $^{99m}TcO_4^-$) uptake to the thyroid gland

1) A patient shall be said to have Graves' disease if he/she has satisfied at least one of the clinical findings and all 4 laboratory findings.
2) A patient shall be said probably to have Graves' disease if he/she has satisfied at least one of the clinical findings and 3 laboratory findings 1 through 3.
3) A patient is suspected to have Graves' disease if he/she has satisfied at least one of the clinical findings and 2 laboratory findings 1 and 2. Elevation in serum FT_4 have usually been present for at least 3 months.

Notes
1. Decrease of serum cholesterol and increase of serum alkaline phosphatase are often observed.
2. There are rare cases with free triiodothyronine (FT_3) elevation alone and normal FT_4.
3. A patient shall be said to have "euthyroid Graves' disease" or "euthyroid ophthalmopathy", if he/she has ophthalmopathy and is positive for TRAb or TSAb, but shows normal FT_4 and TSH.
4. In an elderly patient, clinical symptoms and signs including an enlargement of the thyroid gland, may not be clear.
5. In children, decreased scholastic ability, accelerated growth, restlessness and other symptoms are observed.

4. Essentials of diagnosis

Guidelines for the diagnosis of thyroid diseases (the sixth draft) have been provided by the Japan Thyroid Association.[2)] The association's guidelines for the diagnosis of Graves' disease are cited in Table 1. These guidelines are available at the Japan Thyroid Association's website (http://thyroid.umin.ac.jp/flame.html).

5. Treatment

(1) **Antithyroid drugs**: These drugs are

often used as drugs of first choice for the treatment of Graves' disease in Japan. Usually, methimazole (MMI) with a slightly higher potency is instituted at a dosage level of 15–30 mg/day, followed by a gradual dose reduction over several years. In case of any adverse reaction occurring (except for agranulocytosis) or during lactation, the drug is replaced with propylthiouracil (PTU). Antithyroid drugs are drugs of first choice for pregnant women.

(2) **Radioactive iodine therapy**: Patients in whom antithyroid drugs cannot be used and middle-aged and older patients who respond poorly to the therapy regimens are better indicated for the use of radioiodine. At present, the therapy is feasible at outpatient services. Therapeutic effects become evident about 6 months after the start of medication, with subsequent development of late hypothyroidism in many cases.

(3) **Subtotal thyroidectomy**: This is preferred for refractory juvenile cases of Graves' disease with notable enlargement of the thyroid.

Hashimoto's Disease

1. Pathophysiology

This disease occurs in nearly one out of every ten middle-aged women and is an organ-specific autoimmune disorder with the highest prevalence. The etiology remains unclear, although cellular immunity and antibody-dependent cytotoxicity are generally thought to be involved.

2. Clinical features and physical findings

Firm diffuse enlargement of the thyroid is the only finding if thyroid hypofunction is not present. The disease progresses into hypothyroidism to produce generalized edema, weight gain, subjective symptoms such as fatiguability, sensitivity to the cold and diarrhea, and physical findings such as hoarseness, dry skin, falling of the lateral one-third of both eyebrows, bradycardia, and a prolonged relaxation phase of the Achilles tendon reflex.

Table 2 Guidelines for the Diagnosis of Chronic Thyroiditis (Hashimoto's Disease)

a) Clinical findings
   1. Diffuse swelling of the thyroid gland without any other cause (such as Graves' disease)

b) Laboratory findings
   1. Positive for anti-thyroid microsomal antibody or anti-thyroid peroxidase (TPO) antibody
   2. Positive for anti-thyroglobulin antibody
   3. Lymphocytic infiltration in the thyroid gland confirmed with cytological examination

1) A patient shall be said to have chronic thyroiditis if he/she has satisfied clinical criterion and any one laboratory criterion.

Notes
1. A patient shall be suspected to have chronic thyroiditis, if he/she has primary hypothyroidism without any other cause to induce hypothyroidism.
2. A patient shall be suspected to have chronic thyroiditis, if he/she has anti-thyroid microsomal antibody and/or anti-thyroglobulin antibody without thyroid dysfunction nor goiter formation.
3. If a patient with thyroid neoplasm has anti-thyroid antibody by chance, he or she should be considered to have chronic thyroiditis.
4. A patient is possible to have chronic thyroiditis if hypoechoic and/or inhomogeneous pattern was observed in thyroid ultrasonography.

3. Laboratory findings

(1) **Routine examination**: Increased ESR, elevation in serum γ-globulin (increased ZTT and TTT values), elevations in CPK and LDH, and high serum cholesterol level are noted.

(2) **Endocrine tests**: Free T_3 and free T_4 in serum are lowered and TSH is elevated. Latent hypothyroidism with a normal thyroid hormone level and with elevation in TSH alone is also frequently observed.

(3) **Immunological tests**: Patients are positive for anti-thyroid peroxidase (TPO) antibody and for anti-thyroglobulin (Tg) antibody.

4. Essentials of diagnosis

The diagnosis guidelines (the sixth draft) provided by the Japan Thyroid Association[2] are shown in Table 2. Occasionally, patients may present transient symptoms of thyrotoxicosis, which is called painless thyroiditis.

5. Treatment

Replacement therapy with T_4 preparations is

performed in patients with hypothyroidism. It is a common practice to use a low dose level for initiating T_4 drug therapy, with subsequent gradual dosage increase until serum TSH level becomes normalized. The therapy should be started at a dose level of 12.5μg/day especially in elderly patients and severe cases because of the potential risk of angina pectoris or cardiac failure.

Type 1 Diabetes Mellitus

1. Pathophysiology

The diagnostic criteria and classification of diabetes mellitus into two types depicting disease states — insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) — were revised in 1999 to those classifying the disease into four types based on etiology, i.e., types 1 and 2, other particular mechanisms or disorders (inclusive of genetic abnormalities), and gestational diabetes.

Type 1 diabetes denotes diabetes mellitus, which develops due to destruction of pancreatic β cells. The disease under this category is further classified into type 1A, which arises through autoimmune mechanisms, and type 1B, which is of non-autoimmune nature.

Type 1A disease of autoimmune etiology includes the slow-progressing insulin-dependent diabetes mellitus (SPIDDM) besides the rapid-onset type, which is typical of conventional IDDM. SPIDDM is a disease form that presents clinical features close to type 2 diabetes mellitus but progresses over several years with depression of pancreatic β cell function and ultimately into an insulin-dependent status. In both these forms of type 1A, the anti-islet autoantibody (to be described below) is detected. The anti-islet autoantibody is not demonstrated in cases of type 1B disease.

Recently, attention has been focused on the presence of fulminant type 1 diabetes mellitus in which ketoacidosis develops in a period of several days (mean: 4 days), occasionally taking a fatal clinical course.

2. Clinical features and physical findings

There are no symptoms/findings specific to type 1 diabetes mellitus. Most patients are non-obese, with more severe symptoms of weight loss, polyuria and thirst due to marked hyperglycemia, and are prone to diabetic coma. In fulminant type 1 diabetes mellitus, about 70% of patients develop common cold-like symptoms such as upper abdominal pain, fever, and headache before the onset of diabetes mellitus.

3. Laboratory findings

(1) **Routine examination**: A diagnosis of diabetes mellitus can be established according to the diagnostic criteria for diabetes mellitus. HbA_{1c} is usually elevated but this parameter remains at normal to a slight elevation in cases of the fulminant form of type 1B disease. Exocrine pancreatic enzymes such as elastase I and amylase are elevated in the fulminant form. Acidosis is often present among cases of type 1 disease other than SPIDDM.

(2) **Endocrine tests**: The fasting serum C peptide level ($<$0.5 ng/m*l*) and urinary C peptide output ($<$10μg/day) are lowered due to depressed insulin secretory function. These are not the case with SPIDDM.

(3) **Immunological tests**: Patients with type 1A disease are positive for anti-glutamic acid decarboxylase (GAD) antibody being anti-islet autoantibody, islet cell antibody (ICA), anti-insulin autoantibody (IAA), and IA-2 antibody.[3] Patients with the fulminant form of type 1 diabetes are negative for these autoantibodies. Of human leukocyte antigens, patients often possess HLA-DR4 or -DR9 and are negative for HLA-DR2.

4. Essentials of diagnosis

Anti-GAD antibody can be measured routinely and must be determined positively when type 1 diabetes mellitus is suspected. In the fulminant form, common cold-like symptoms frequently precede the onset of the disease,

so urine tests for glucose (and ketones) are essential in patients with colds complaining of lassitude.

5. Treatment

Usually, an intensive insulin therapy regimen consisting of a dose of a regular (or rapid-acting) insulin is undertaken before every meal and a dose of an intermediate-acting (or long-acting) insulin at bedtime. If the blood glucose level is still poorly controlled with this regimen, then continuous subcutaneous insulin infusion (CSII) is performed. It has been shown that low-dose insulin provides a protective effect for pancreatic β cells, and replacement with insulin therapy is required in patients with SPIDDM receiving sufonylureas.

Addison's Disease

1. Pathophysiology

Addison's disease is caused by destruction of the adrenal cortices resulting in chronic adrenocortical insufficiency. Leading causes are autoimmune destruction, termed idiopathic, and tuberculosis. In the idiopathic entity, the disease may present polyglandular autoimmune syndrome involving complications by other organ-specific autoimmune disorders (i.e., type 1 diabetes mellitus, Hashimoto's disease, idiopathic hypoparathyroidism, gonadal hypofunction, mucocutaneous candidiasis, and pernicious anemia). These are classified into type I caused by juvenile-onset autoimmune regulator (AIRE) gene abnormality, type II, being an adult-onset disease without associated non-endocrine disorder, and type III, which does not involve Addison's disease.[4)]

2. Clinical features and physical findings

Hyperpigmentation due to increased secretion of ACTH is a characteristic clinical feature. Aldosterone-cortisol-adrenal androgen deficit symptoms are also noted.

3. Laboratory findings

(1) **Routine examination**: Hypoglycemia, hyponatremia, hyperkalemia, and peripheral blood eosinophilia are present.

(2) **Endocrine tests**: Diagnostic findings include elevated plasma ACTH, low plasma and urine cortisol levels, low plasma aldosterone level, low plasma DHEA-S value, decrease in urinary 17-OHCS/17-KS, and no or low plasma cortisol in the rapid ACTH test.

(3) **Immunological tests**: Autoantibodies recognizing steroid-synthesizing enzymes are detected but these laboratory tests have not been generally adopted to date.

4. Essentials of diagnosis

When there are diverse nonspecific symptoms, the disease must be deduced from skin pigmentation and routine laboratory test data. Caution must be exercised because if the disease is left undiagnosed and without adequate steroid substitution therapy, some types of stress may precipitate adrenal crisis (acute adrenal insufficiency) with a fatal outcome.

5. Treatment

Replacement therapy with hydrocortisone at 20 mg/day is a common practice. A divided dose in the morning may be greater than the one given in the early evening to be in harmony with circadian rhythm in cortisol secretion. The dose of hydrocortisone should be raised 2- to 3-fold the usual dose (40–60 mg/day) in case of common cold with pyrexia or other infections, trauma, or surgery.

Conclusions

Endocrine diseases in which autoimmune mechanisms are considered to be involved, besides the four above-mentioned diseases, include lymphocytic adenohypophysitis, lymphocytic infundibuloneurohypophysitis, and idiopathic hypoparathyroidism. Autoimmune endocrine disorders are most frequent among various autoimmune diseases, so it is of importance to always keep this fact in mind in daily

clinical practice to achieve diagnosis and treatment in such cases.

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Autoimmune Neurological Diseases

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Abstract: Multiple sclerosis, myasthenia gravis, and Guillain-Barré syndrome are neurological diseases induced by abnormal autoimmunity. Since these diseases show characteristic clinical courses and neurological symptoms, they can be diagnosed with appropriate examinations. However, it is necessary to note that the common types of these diseases in Japan are not always the same as those in Western countries. Based on an increasing knowledge of the pathological mechanisms of the diseases, various immune therapies are being developed.

Key words: Autoimmune neurological diseases; Multiple sclerosis; Myasthenia gravis; Guillain-Barré syndrome

Introduction

This paper describes some representative autoimmune neurological diseases. As described later, the common types of the diseases in Japan are different from those in Western countries; for example, the optic-spinal form of multiple sclerosis and the axonal form of Guillain-Barré syndrome are more common in Japan than in Western countries. This suggests that the development of autoimmune neurological diseases varies among races and is substantially influenced by environmental factors. Therefore, care is needed in interpreting medical textbooks and literature published in Western countries.

Multiple Sclerosis

The diagnosis of multiple sclerosis (MS) is made according to the conventional clinical description of "spatially and temporally separated multifocal central nervous lesions".[1] Pathologically, MS presents perivascular inflammation and myelin sheath destruction (demyelination plaques) in the white matter.

The prevalence of the disease in Caucasians is 40 to 100 per 100,000 individuals, while it is only about one-tenth of this figure among the Japanese. The disease type is also different between Caucasians and Japanese — the cerebral and optic-spinal forms are predominant in the former and the latter, respectively.

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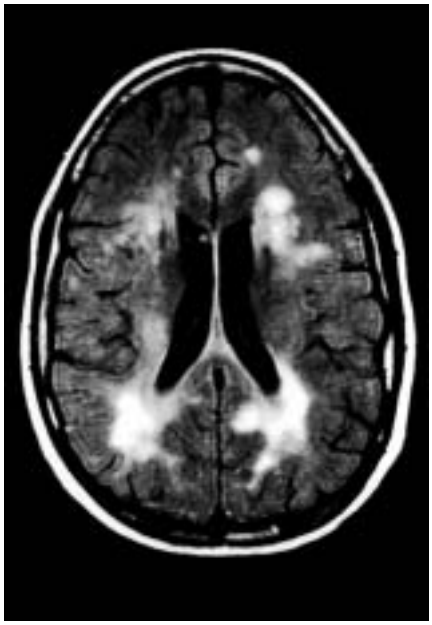

Fig. 1 Head MRI (FLAIR) image of a patient with multiple sclerosis: multiple high-density areas are observed in the white matter around the lateral ventricles.

1. Diagnostic examination

MRI shows demyelination plaques in the white matter around the cerebral ventricles, brain stem, cerebellum, and spinal cord as high signal intensity areas in T2-weighted or fluid attenuated inversion recovery (FLAIR) images (Fig. 1). However, attention should be paid to the fact that similar findings may also be observed in patients with other inflammatory diseases, ischemia, metabolic diseases, and tumors.

Cerebrospinal fluid examination shows increased IgG in about 70% of the patients, with a resultant increase of the IgG index (obtained by dividing the ratio of IgG to albumin in the cerebrospinal fluid by the corresponding ratio in the serum). The positive rate of oligoclonal bands of about 35 to 46% in Japanese patients is lower than in Westerners. Furthermore, although the number of cells in the cerebrospinal fluid of MS patients should be less than $50/mm^3$, the cell numbers exceed $50/mm^3$ in a considerable number of Japanese patients.

The examination of evoked potential is useful for detecting clinically asymptomatic potential lesions that cannot be read in MR images. It is performed for visual, auditory, and somatic sensation — when any of the sensory pathways is abnormal, its signal latent time is prolonged.

2. Clinical course

MS mainly develops in patients in their twenties to fifties, with a peak being noted between 25 and 30 years. Most patients are classified into relapsing/remitting MS in which periods of exacerbation and periods of stable or improved clinical state occur alternately. Symptoms may recur from several times a year to only once every several years.

Primary progressive MS that progresses chronically from the onset has been reported in about 10 to 15% of Western patients,[2] but only in 5% of Japanese patients. This form of MS has to be differentiated from neurodegenerative diseases or cerebral tumors.

In about 10% of patients with relapsing/remitting MS, the disease gradually becomes progressive within 10 years (secondary progressive MS). Although this form of MS is observed in 20 to 40% of patients in Western countries, it is less frequently observed in Japan.

3. Neurological symptoms

MS has a large variety of neurological symptoms. It often occurs with vision disorder or acute transverse myelitis in Japanese because many Japanese MS patients are classified into optic-spinal MS. The symptoms that may develop during the clinical course of MS include reduced vision, double vision, dyskinesia/paresthesia, spasm, dysuria, ataxia, tremor, cognitive dysfunction, and Lhermitte's sign (an electric shock-like sensation running from the back to the limbs when the neck is bent forward, and associated with lesions in the cervical-spinal cord posterior funiculus). In addition, paroxysmal symptoms may occur,

including trigeminal neuralgia, paroxysmal articulation disorders, and dystonic paroxysm (often called tonic convulsions).

4. Treatment

Adrenocortical steroids have long been used for the treatment of relapsing/remitting MS. The most reliable therapy is the intravenous drip infusion of 1,000 mg of methylprednisolone (for 3 days), followed by the oral administration of prednisolone. Although these steroids shorten the periods of administration or symptomatic relapse, they do not reduce the relapse rate or change the long-term prognosis. Plasmapheresis may be effective for patients who do not respond to a massive dose of methylprednisolone.

Amantadine and selective serotonin reuptake inhibitors serve as useful symptomatic treatment for relieving fatigue. Carbamazepine is often effective for trigeminal neuralgia and Lhermitte's sign. Carbamazepine or phenytoin is used to treat dystonic paroxysm.

Interferon β-1b (Betaferon®) was approved in Japan in September 2000 for relapsing/remitting MS and secondary progressive MS to reduce the relapse rate. It is also effective for optic-spinal MS. It is used by subcutaneously injecting 8 MIU (million international units) every other day. It has been reported to cause adverse effects such as influenza-like symptoms, redness/pain/necrosis at the injection site, and depression.

Myasthenia Gravis

The prevalence rate of myasthenia gravis (MG) has been reported to be 5 to 7 per 100,000 people. It occurs relatively frequently in females in their twenties and thirties, but tends to more frequently occur in males in their forties or older.

1. Clinical symptoms

The most evident symptom is tiring easily. The repeated use of muscles causes muscular weakness, which quickly becomes evident as fatigue. The fatigability may be improved by taking a rest. In addition, MG is subject to intraday or interday variation (for example, it is more severe in the evening than in the morning).

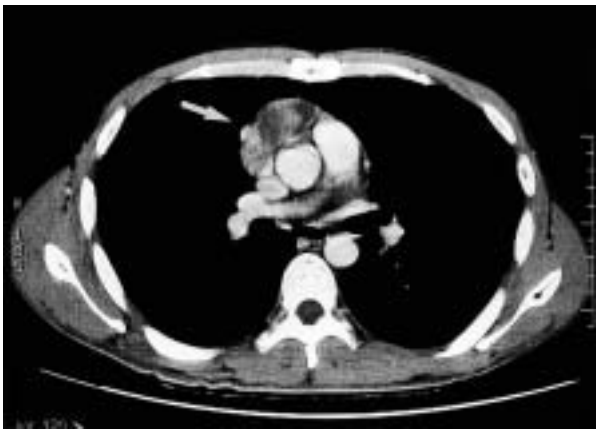

Fig. 2 Chest CT of myasthenia gravis. Thymoma (arrow) is apparent in the anterior mediastinal region.

MG often develops with blepharoptosis and double vision owing to extraocular muscle weakness, although it may develop with bulbar paralysis (articulation disorders and dysphagia) or muscular weakness of the limbs (with proximal muscles being dominant). The symptoms are not always symmetrical.

2. Diagnosis

(1) A diagnostic test is performed with edrophonium hydrochloride (Tensilon®), a short-acting anticholinesterase agent. Its solution (dissolved in 9 m*l* of physiological saline at 10 mg/m*l*) is intravenously administered to determine whether it improves muscular weakness or not.

(2) A repeated stimulation test using a surface electromyogram is performed at 1, 3, 5, 10, and 20 Hz. The patients with MG show a waning phenomenon (reduced amplitude of provoked potential as compared with the first trial) in response to either high or low frequency stimuli.

(3) A blood test is performed for anti-acetylcholine receptor antibody. The antibody is positive in about 80% of MG patients, although the antibody titer does not always correlate with the severity of the disease.

(4) Imaging diagnosis (CT or MRI) is performed for the anterior mediastinal region because MG is often complicated with thymoma or thymic hyperplasia (Fig. 2).

3. Treatment

An appropriate treatment should be selected, depending on the symptoms of each patient. Basically, MG is treated with anticholinesterase agents or adrenocortical steroids to be administered every other day, or thymectomy. Oral anticholinesterase agents, such as Mestinon® and Mytelase®, inhibit acetylcholinesterase, and mild MG may be resolved with anticholinesterase therapy alone.

However, they do not treat the basic mechanism of MG lesions, that is, they are not effective for the actions of the autoantibodies against postsynaptic receptors or adjacent muscle membrane. Therefore, an adrenocortical steroid is administered every other day for MG, except the ocular muscle form. It is started at a dose of 20 to 30 mg/day and maintained at 60 to 100 mg/day for several weeks followed by gradual dose reduction.

Immunosuppressive agents such as azathioprine and cyclosporin can be used in intractable cases that do not respond to anticholinesterase agents or adrenocortical steroids. (These immunosuppressive agents are not covered by the Japanese medical insurance scheme.)

In September 2000, tacrolimus (Prograf®) was approved for coverage by Japanese medical insurance for patients who do not respond well to steroids or for whom steroids are contraindicated. A recent study reported that the drug was markedly effective in some cases.[3)]

Plasmapheresis or massive γ-globulin administration (intravenous immunoglobulin: IVIG) is performed in severe cases or in those who developed a crisis. The effects of plasmapheresis are not significantly different between the double filtration and immune adsorption techniques. IVIG is generally administered at 400 mg/kg for 5 days.

Thymectomy is essential for patients with thymoma. In patients without thymoma, residual fat tissue in the anterior mediastinal region is removed.

Guillain-Barré Syndrome

It is important to differentiate the demyelinating and axonal forms of polyneuropathy by performing a nerve conduction test and checking for F wave abnormality. The most common type of demyelinating polyneuropathy results from the inflammation of myelin sheaths and is therefore called inflammatory demyelinating polyneuropathy. Its acute form is Guillain-Barré syndrome (GBS). It should be noted that GBS is different in Japanese and Westerners — the axonal form accounts for about 30% in Japanese patients.

1. Clinical course and prognosis

In typical patients with GBS, tetraplegia rapidly progresses and the progression stops within 4 weeks. After an average plateau period of 2 weeks, the patients start to recover. However, some patients may show different clinical courses, including the suspension of the progression, phased exacerbation of tetraplegia, and recurrence of symptoms during recovery.

Although plasmapheresis and IVIG, which are described later, may modify these clinical courses, the prognosis of GBS is poor in the elderly, patients with rapidly progressing symptoms, those requiring artificial respiration, and those with electrophysiologically low amplitude of complex muscular action potential. Further, the patients with axonal GBS generally have a poorer prognosis than those with demyelinating GBS.

Although more than 75% of GBS patients have complete functional recovery within 6 months of its onset, about 15% have sequelae that limit daily activities. GBS recurs infrequently, with a recurrence rate of 5% or lower.

2. Etiology and mechanism

About two-thirds of patients with GBS have a history of prior infections (such as upper respiratory inflammation or diarrhea). The pathogens involved include *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr (EB) virus, mycoplasma, HIV, and influenza bacillus.

The most common in Japan is infection with *C. jejuni*, which is an important bacterium responsible for bacterial diarrhea. It should be noted that GBS associated with *C. jejuni* infection is frequently observed in China. GBS associated with *C. jejuni* often develops as a purely motor axonal form.[4)]

The annual prevalence of GBS in Japan is 1 to 2 individuals per 100,000, which is comparable to that in Western countries.

3. Treatment

The main treatment for GBS is to remove anti-ganglioside antibodies and TNF-α, which are considered to be involved in the onset of GBS and increase in the acute phase of the disease. Adrenocortical steroid therapy had previously been used, but it was proved ineffective when administered alone. Therefore, plasmapheresis, IVIG, and pulse therapy with methylprednisolone are currently used. Other standard treatments include those for respiratory disorders, arrhythmia, abnormal blood pressure, and complications such as infections and pulmonary infarction, as well as rehabilitation during the recovery phase.

Plasmapheresis is roughly divided into simple plasmapheresis, plasmapheresis based on double filtering, and plasma adsorption using an immune adsorber. Plasmapheresis inhibits exacerbation, shortens the morbid period (including artificial respiration period or period until the patient can walk), and relieves sequelae.

Table 1 Hughes' Functional Grade

Grade 0	Normal
Grade 1	Has mild neurological symptoms
Grade 2	Can walk for 5 meters without a cane
Grade 3	Can walk for 5 meters with a cane or supporting device
Grade 4	Is restricted to bed or wheelchair
Grade 5	Requires assisted ventilation
Grade 6	Dead

Plasmapheresis is generally indicated for the following patients:

(1) Patients with moderate or severe symptoms (Grade 4 or higher as evaluated with the Hughes' functional grade (Table 1)) or those classified into Grade 3 who have progressive muscular weakness
(2) Patients within 14 days of onset
(3) Patients without serious circulatory, renal or hepatic diseases
(4) Patients at 16 years old or older without septic shock, a history of myocardial infarction within 6 months, marked autonomic disorder, or tendency to hemorrhage.

The following frequency is considered appropriate for plasmapheresis depending on severity.[5)]

(1) Two times for mild patients (who can walk and stand, but cannot run)
(2) Four times for moderate patients (who need assistance standing) and severe patients (who need artificial respiration)

Any of the above plasmapheresis techniques usually improves GBS symptoms and suspends the progression of GBS within one week after the start of the treatment.

IVIG has been demonstrated to improve motor function, shorten the morbid period, and reduce the rate of patients who need artificial respiration 4 weeks after the start of the

Fig. 3 General guide to Guillain-Barré syndrome

treatment. IVIG is expected to provide an almost comparable effect to plasmapheresis. IVIG is performed by intravenous drip infusion of 400 mg/kg/day of a human immunoglobulin preparation (Venilon-I®) for 4 to 6 hours once daily for 5 straight days.

The pulse therapy with methylprednisolone is not effective when given alone. However, it has been reported to improve motor function at week 4 or to shorten the period until independent gait when combined with IVIG. The pulse therapy is performed by the intravenous drip infusion of 500 mg/day of methylprednisolone together with human immunoglobulin preparation for 5 days continuously.

Because of the low prevalence rate, it is difficult for patients and their families or other people, including paramedical staff, to obtain detailed information on GBS. With support from the Guillain-Barré Syndrome Foundation International, an international GBS organization, we have prepared a General Guide to Guillain-Barré Syndrome (Fig. 3), which is available at no cost.

Conclusion

This paper discussed three autoimmune neurological diseases, multiple sclerosis, myasthenia gravis, and Guillain-Barré syndrome. We would like to emphasize again the importance of understanding their specific characteristics in Japanese patients in order to provide appropriate treatment.

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Autoimmune Diseases in Dermatology

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Abstract: This article summarizes the concept, clinical characteristics, and treatment of bullous diseases and erythema nodosum, which are typical autoimmune diseases in the field of dermatology. Autoimmune bullous diseases are classified into the pemphigus group, with antibodies against substances between epidermal cells, and the pemphigoid group, with antibodies against epidermal basement membrane. The causative antigens for each group have recently been identified. Type-III allergic reaction induced by bacteria, medicine, etc. as causative antigens is thought to be involved in the development of erythema nodosum. The treatment of the diseases chiefly consists of removal of causative antigens and steroid hormone therapy.

Key words: Pemphigus; Bullous pemphigoid; Erythema nodosum; Autoimmune disease

Autoimmune Bullous Diseases

1. Concept

In autoimmune bullous diseases, antibodies against epidermal antigens damage the epidermis, resulting in bullous formation. Autoimmune bullous diseases are divided into two groups: the pemphigus group with antibodies against substances between epidermal cells, and the pemphigoid group with antibodies against epidermal basement membrane.

Desmosome and hemidesmosome are considered to play important roles in the adhesion of epidermal cells. Recent molecular-biological studies have shown that the antigens of all autoimmune bullous diseases are the components of desmosome and hemidesmosome. Figures 1 and 2 show the structure and component proteins of hemidesmosome and desmosome, respectively.

Desmosome exists in epidermal cell membrane. Keratin intermediate-sized filaments combine with the intracellular adhesion plate. Two membrane proteins of desmoglein and desmocollin maintain intercellular adhesion, each of which is subdivided into Types 1 to 3. Intracellular adhesion is based on desmoplakin (DPL), envoplakin (EPL), periplakin (PPL), placoglobin (PG), and placophilin. Types 1 and 3 desmoglein are the target antigens of pemphigus.[1–3)]

Keratin intermediate-sized filaments also combine with the adhesion plate of hemidesmosome. Intracellular adhesion plate pro-

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teins include BP230 and plectin that belong to the plakin family. Trans-membrane proteins include BP180 and $\alpha 6\beta 4$ integrin. BP180 and BP230 are the target antigens of bullous pemphigoid.[1,4)]

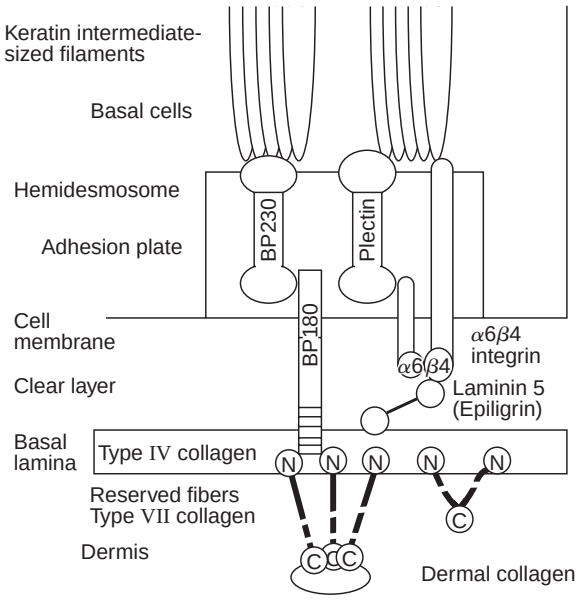

Fig. 1 Structure of hemidesmosome (see Reference 1)

2. Pemphigus

(1) Definition and classification

Pemphigus is a representative autoimmune dermal disease associated with autoantibodies against substances between epidermal cells. It is divided into four classic types — pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, and pemphigus erythematosus — as well as other types of herpetiform, drug-induced, tumor-associated, and IgA pemphigus. The antigens of each type of pemphigus are listed in Table 1.

(2) Clinical symptoms and pathological findings

Pemphigus vulgaris often develops as intractable diffuse oral lesions, followed by loose bullae and erosions on the skin (Fig. 3). The bullae and erosions tend to develop at intertriginous sites and be epithelialized without scarring.

Pemphigus vulgaris is associated with the bullous formation on mechanically stimulated normal skin, which is called "Nikolsky's sign." Histopathologically, acantholysis (epidermal cells are separated from each other to form

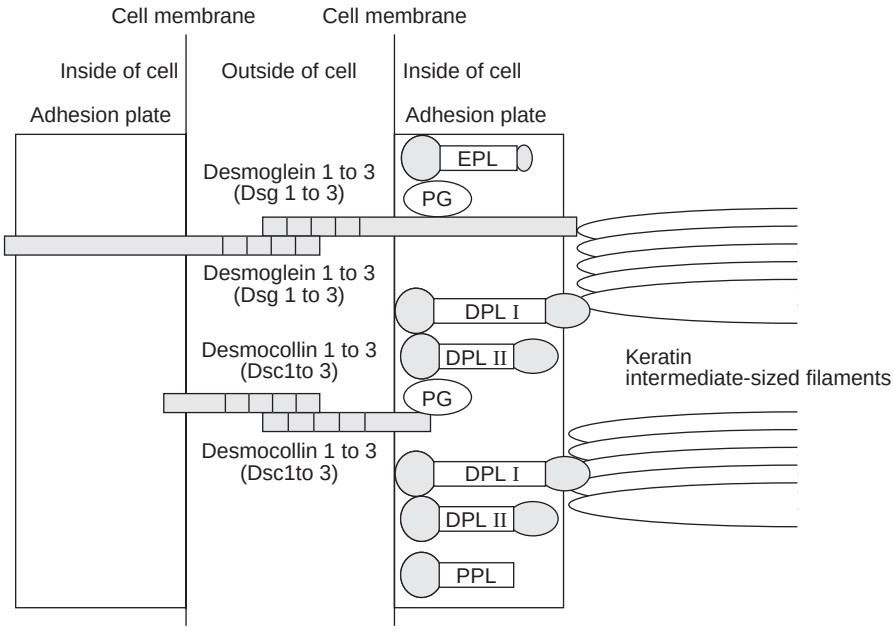

Fig. 2 Structure of desmosome (see Reference 1)
(EPL: Envoplakin, PG: Placoglobin, DPL: Desmoplakin, PPL: Periplakin)

Table 1 Classification and Antigens of Pemphigus

Subtype	Immunoglobulin	Antigen
Pemphigus vulgaris	IgG	Desmoglein 3 (DG3)
Pemphigus vegetans	IgG	DG3
Pemphigus foliaceus	IgG	DG1
Pemphigus erythematosus	IgG	DG1
Herpetiform pemphigus	IgG	DG1 (DG3)
Drug-induced pemphigus	IgG	Various
Tumor-associated pemphigus	IgG	Desmoplakin, envoplakin, periplakin, BP230, DG1 and 3, and 170 kDa protein
IgA pemphigus	IgA	Desmocollin 1

(Quoted from Hashimoto, T.: Hydroa. *Easy Dermal Immunology* (Nishioka, K. ed.) 2002; pp. 199–208) (in Japanese)

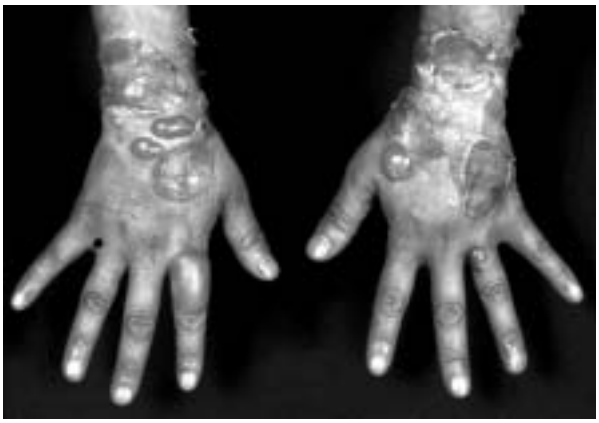

Fig. 3 Clinical case with pemphigus vulgaris

intraepidermal bullae) is observed over the basal layer. Skin biopsy using a fluorescent antibody technique shows the deposition of IgG and C3 between epidermal cells.

Pemphigus vegetans is a subtype of pemphigus vulgaris and appears as a verruciform skin elevation associated with epidermal hypertrophy by the long-term mechanical stimuli at intertriginous sites.

Pemphigus foliaceus causes shallow erosions, squamae, and crusts at seborrheic sites of the head, face, chest, and back. The erosions are quickly resolved, although pigmentation remains. This type of pemphigus is usually not associated with oral lesions.

Pemphigus erythematosus is a subtype of pemphigus foliaceus. It causes exanthema at seborrheic sites as in pemphigus foliaceus. Furthermore, it causes a butterfly erythema associated with keratose erosions on the face. It may be positive for antinuclear antibodies and complicated with thymoma. The biopsy of pemphigus foliaceus and erythematosus shows subcorneal bullae associated with acantholysis.

(3) **Diagnosis**

Pemphigus can be easily diagnosed based on clinical symptoms, histopathological examination, fluorescent antibody technique, and enzyme-linked immunosorbent assay (ELISA). It has to be differentiated from other autoimmune bullous diseases, drug eruption, and impetigo contagiosa.

(4) **Treatment**

Pemphigus vulgaris or vegetans should be treated with steroid hormones at an initial dose of 40 to 60 mg/day (the dosage is based on predonisolone®). If the disease does not respond, the dose should be increased 1.5 to 2 times or steroid pulse therapy performed. Previous studies reported that the combination with immunosuppressive agents (such as cyclosporin and MTX), plasmapheresis, and massive γ-globulin therapy was effective for

intractable pemphigus. Pemphigus foliaceus often requires a smaller oral dose of steroid hormone than pemphigus vulgaris: an initial dose of 20 to 40 mg/day (based on predonisolone®) may be enough.

3. Bullous pemphigoid

(1) **Concept and definition**

Bullous pemphigoid is an autoimmune bullous disease in which autoantibodies react with 230 kDa and 180 kDa pemphigoid antigens in hemidesmosome to cause subepidermal bullae. Tense and filled bullae on severely itching edematous erythema in the elderly clinically characterize the disease.

(2) **Clinical symptoms and pathologic findings**

As described above, bullous pemphigoid tends to develop in the elderly. At first, urticaria-like or exudative erythema associated with severe systemic itching develops, followed by the gradual formation of tense and filled large bullae on erythema. The bullae, when ruptured by scratching, cause erosions that look like burns on the whole body. Severe bullous pemphigoid may be complicated with fever, body weight loss, and anemia. Histopathologically, subepidermal bullae associated with eosinophilic and neutrophilic infiltration characterize the disease. Fluorescent antibody technique shows the linear deposition of IgG and C3 along the basement membrane.

(3) **Treatment and prognosis**

Mild bullous pemphigoid may be resolved only with the external application of steroid hormone. However, the disease is basically treated with the oral administration of steroid hormone: an initial dose of 40 mg/day (based on predonisolone®) is often used. Sulfa agents, such as diaminodiphenyl sulfone (DDS) and diaphenylsulfone (Lectisol®), or the combination therapy of minocycline and nicotinamide have been reported to be effective.

The prognosis of the disease is good, and the disease can be controlled with the oral administration of steroids. However, since many patients with the disease are elderly, attention should be paid to possible infections and malignant tumors.

Erythema Nodosum

1. Concept

Erythema nodosum is a painful erythema that develops on the extensor side of the leg. Histologically, septal panniculitis at the septum between subcutaneous fat and connective tissue characterizes the disease.

2. Etiology

Etiologic factors of erythema nodosum include infection with bacteria including *hemolytic streptococcus, Mycobacterium tuberculosis, Mycobacterium leprae*, and viruses, as well as drugs, Behçet's disease, sarcoidosis, and ulcerative colitis. Among them, the infection with *hemolytic streptococcus*, such as tonsillitis, is considered the most important factor. Although it has been suggested that Type III allergic reaction to these antigens may be involved in the development of the disease, this hypothesis has not been fully examined. Erythema nodosum is considered to occur in 10 to 15% of patients with Sweet's disease and 80% of those with Behçet's disease.

3. Clinical symptoms

Erythema tends to occur on the extensor side of the leg, although it may occur on the femoral region and forearm. Erythema appears as a painful and poorly defined mild elevation at which subcutaneous induration is palpable (Fig. 4). It is associated with heat, but not with erosions and ulcers. Erythema disappears in several weeks, but pigmentation remains. It is often associated with fever and may be associated with articular pain of the knee.

4. Histopathological findings

Making a diagnosis of erythema nodosum needs a skin biopsy to histopathologically examine the erythematous lesion. The lesion extends from the dermal substratum to sub-

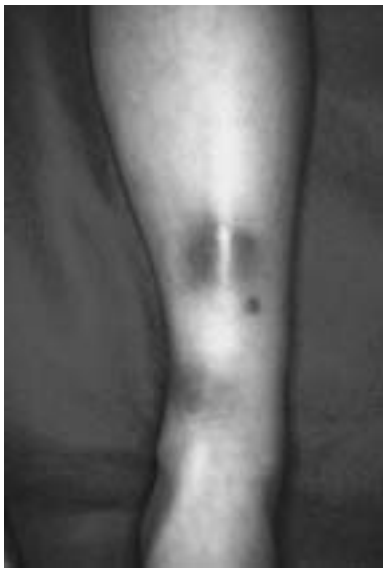

Fig. 4 Clinical case with erythema nodosum

cutaneous tissue and mainly results from septal panniculitis or inflammation of fat tissue at the septum with connective tissue. In the early stage, the disease shows neutrophilic and lymphocytic infiltration and fibrin precipitation in fat tissue. It then gradually presents chronic granulomatosis-like findings, such as infiltration of histiocytes and giant cells, hyperplasia of capillary vessels, and increase in fibroblasts.

5. Laboratory findings

Erythema nodosum is associated with inflammatory findings including increased white blood cell count, blood sedimentation rate and CRP. Increased ASO and ASLO are observed in patients infected with *hemolytic streptococcus*.

To examine the possible complication by pulmonary tuberculosis and sarcoidosis, it is also necessary to perform chest X-rays and a tuberculin test.

6. Diagnosis and differentiation

Any painful erythema associated with subcutaneous induration on the leg has to be pathologically examined with skin biopsy to differentiate it from the following diseases.

(1) **Erythema induratum (Bazin)**

This type of erythema can be clinically differentiated by ulcerative erythema on the leg with persistent scars. Histopathologically, the diagnosis of the disease can be made with histological findings of lobular panniculitis, in which inflammation occurs mainly in fat tissue lobules, and epithelioid cell-like granuloma and caseation necrosis.

(2) **Thrombophlebitis**

Restiform induration clinically characterizes thrombophlebitis. This disease can be histopathologically differentiated from erythema nodosum.

(3) **Periarteritis nodosa (cutaneous type)**

Subcutaneous induration consistent with the crossings of livedo reticularis clinically characterizes the disease. Pathologically, this disease appears as necrotic angitis.

7. Treatment

Erythema nodosum improves only by elevating the leg and allowing the patient to rest. At first, an infectious focus of tonsillitis is located. When an infection with *hemolytic streptococcus* is suspected, it is necessary to administer a penicillin antibiotic. An underlying disease such as tuberculosis, fungal infection, sarcoidosis, or Sweet's disease, if any, is treated. Temporary systemic administration of steroid hormone is attempted in patients with severe fever and arthralgia without infectious focus and underlying disease, although this should be done carefully.

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Current System for Regulation of Health Foods in Japan

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Abstract: The current Japanese system for regulation of "health foods" calls them "Foods with Health Claims" and divides them into two categories. One is "Foods with Nutrient Function Claims." The label can be freely used if a product satisfies the standard for the minimum and maximum daily levels of consumption. Twelve vitamins and five minerals are presently standardized. The other is "Foods for Specified Health Uses." They contain dietary ingredients that have beneficial effects on physiological functions of the human body to maintain and promote health and to improve health-related conditions. Health claims for these foods correspond to the enhanced or "other" function claims of Codex Alimentarius or structure/function claims of the United States. However, disease risk reduction claims are not allowed. After the Food Safety Commission examines the safety of the product and the Pharmaceutical Affairs and Food Sanitation Council evaluates the effectiveness, the Ministry of Health, Labor and Welfare gives official approval, allowing the manufacturer to carry the structure/function claims and mark on the product. In order to maintain and improve people's health and to prevent chronic non-communicable diseases, a well-balanced diet is much more important than "health foods," including "Foods with Health Claims."

Key words: Dietary supplement; Foods with health claims; Foods with nutrient function claims; Foods with specified health uses; Disease risk reduction claims

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The Japanese text is a transcript of a lecture originally aired on June 13, 2001, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

Introduction

The purpose of the present paper is to describe the current regulatory system for "health foods" in Japan. In 2004, however, the system may be amended based on the report of the Advisory Committee of the New System for Regulation of "Health Foods" (Chairman: H.T.), the Japanese Ministry of Health, Labor and Welfare (called the Ministry of Health and Welfare until 2001). Some points that were being debated by the Committee will also be mentioned in this paper.

The term "health food" is often used in Japan, although a clear definition of "health food" has not been established.[1)] According to the US Dietary Supplement Health and Education Act (DSHEA) of 1994,[2)] dietary supplements can be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. On the other hand, Japanese "health foods" can not only be produced in forms that resemble drugs, but may also take the form of conventional or processed foods such as 'tofu' (bean curd), noodles, Hamburg steak, sausages, crackers, yogurt, beverages and confectionery. The difference in forms is the main reason why the term "health food" is used instead of dietary supplement in Japan. There is no major difference in the dietary ingredients of the two. As defined in the DSHEA,[2)] a "health food" is a product taken orally that contains a dietary ingredient intended to supplement the diet. The dietary ingredients in these products may include: vitamins, minerals, amino acids or proteins, fatty acids or oil, herbs or other botanicals, and substances such as enzymes, organ tissues, glandulars, and metabolites. "Health food" is a generic term for food products, whether foods, drinks or dietary supplements, that carry nutrient function and health claims or that are designed to be more effective than common foods in helping people maintain and promote their health, or at least are expected to have such an effect.[1)] But "health foods" do not include organically produced foods.

A Tentative Classification of "Health Foods"

Primitive humans, who evolved approximately 1 million to 200,000 years ago, gathered wild plants, animals, and minerals that they knew to be edible through experience.[1,3)] Then our ancestors deliberately cultivated and domesticated particular species of plants and animals. Processed foods were also introduced in order to preserve food quality, achieve more complete use, and provide a stable supply of foodstuffs. Recently, recombinant gene technology has allowed the creation of new species, giving rise to plants rich in β-carotene and other special nutrients (enriched products), and even cloned cows. We prepare these conventional foods for eating by boiling, broiling, frying, and seasoning them. We usually eat cooked foods.

A conventional food contains more than one nutrient. "Health foods" that are rich in a specific nutrient are identified, and then many nutrient-products are made by extraction, fermentation, enzyme activation and synthesis. If they are found to have physiologically active functions other than nutrient functions, e.g., antioxidation or immune system enhancement, they are recognized as a group of "health foods" (1 in Table 1) and authorized as "Foods with Nutrient Function Claims" in Japan.[4)]

A conventional plant food generally has two components: nutrients and non-nutrients. Among non-nutritive components are chlorophyll, isoprenoids or terpenoids, tannins, steroids, flavonoids, carotenoids, organosulfur compounds, organic acids and others that can have physiological effects beyond the traditional nutritional effects: immunity enhancement, antioxidation, anticoagulation and others, or the reduction of the risk of a disease. These fall under the second group of "health foods" called biogenics, a kind of functional food [2-2)

Table 1 Biologically Active Ingredients in "Health Foods" Used Mainly in Japan

1. Nutrient	
1) Nutrient function	Vitamin. Mineral. Protein.
2) Other function	Vitamin C, E (Antioxidation). Rice, wheat, barley and adlay germ. Branched chain amino acid. Lacto-tripeptide, sardine-peptide and oligo-peptide from dried bonito (Inhibitor of angiotensin converting enzyme). EPA, DHA, α-, γ-linoleic acid, oleic acid, diacylglycerol, and medium chain fatty acid. Coenzyme Q10
2. Non-Nutrient	
1) Prebiotics	Dietary fiber (Indigestible dextrin, blond psyllium husk, algin, etc.). Polysaccharide (Chitosan, glucosamine, chondroitin, etc.). Oligosaccharide (Lacto-sucrose, fructo-oligosaccharide, galacto-oligosaccharide, lactulose, etc.). Sugar alcohol (Xylitol, maltitol, lactitol, sorbitol, mannitol, etc.).
2) Biogenics (Phytochemicals)	Isoprenoid (Glycyrrhizin, triterpenoid saponins in Panax ginseng, gymnema, etc.). Tannin (Catechin in green tea, etc.). Steroid (Sitosterol, etc.). Flavonoid (Flavonoid glycoside in ginkgo leaf, daidzin, genistein, etc. in soy, anthocyanin in blueberry, etc.). Carotenoid (α-, β-carotene in palm kernel oil, etc.). Organosulfur compound (Alliin, allicine, etc. in allium vegetables, etc.). Organic acid (Hydroxycitric acid in garcinia, etc.). Chlorophyll (Chlorophyll in chlorrella and spirulina, etc.).
3. Specific ingredient (Crude drug origin)	Anthraquinones in Aloe arborescens natalenis and Aloe vera. Curcumin in turmeric. Hypericin in St. John's wort. Betaine, zeaxanthin, beta-sitosterol, etc. in dried berries and root bark of lycium. Gutta-percha, eucommial, etc. in bark of Eucommia ulmoides, etc.
4. Multiple ingredients	
1) Plant origin	Agaricus blazei, Ganoderma lucidum, Phellinus linteus, Zizania latifalia, kale, saw palmetto, prune, raspberry, fucoidan, etc.
2) Animal origin	Royal jerry, propolis, etc.
3) Mineral origin	Bittern, etc.
5. Probiotics and microorganisms	Lactobacillus, bifidobacterium, etc. Beer yeast, Bacillus subtilis natto, etc. Jar vinegar, husked rice vinegar, etc.

in Table 1].

Prebiotics and probiotics are the third group of "health foods," some of which are legally approved as "Foods for Specified Health Uses" or "foods with structure/function claims[2] or enhanced or 'other' function claims[5]" in Japan.[6–8] A prebiotic is defined as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon [2-1) in Table 1], and a probiotic is defined as a live microbial food ingredient that is beneficial to health (5 in Table 1).

Drugs and foods share the same origin. The Chinese concept that medicine and food are essentially the same may be partly based on this fact.[1,3] While humans were hunting wild animals and gathering plants and minerals for food, they discovered roots, leaves, and barks of plants (medicinal herbs), organs and tissues (including stones) of animals, and some minerals that were effective against diarrhea, pain, bleeding, etc. Our ancestors collected and stored such useful natural products. Also, information about useful natural products was passed from generation to generation in different areas and by different ethnic groups. It was in China that herbal medicines or Chinese medicines were developed, and some books on them were written between the first and third centuries.[1,9] They have been widely used as crude drugs in Japan as well as in China since that time. With the technological progress of science in the 20th century, it was found that some of them had specific components with

medicinal effects, which were neither nutritive nor non-nutritive. The specific components and their derivatives were isolated and purified, and became ethical drugs: morphine was obtained from opium, quinine from cinchona, salicin (its derivative is acetyl salicylic acid) from the bark of certain poplars and willows, steroids from animal adrenal cortex, prostaglandins from semen, etc.[9] In 1971, the Director of the Pharmaceutical Bureau, the Ministry of Health and Welfare, issued the notification, "Instruction and Regulation for Disapproval Drugs," in which approximately 170 ingredients that originated from plants and animals were defined as foods, because they were mildly effective and probably safe.[10] Hence, as long as indications and actions are not claimed, they are not regarded as drugs. They are the fourth group of "health foods" (3 in Table 1).

The fifth group is complicated (4 in Table 1). There are some food products that originate in natural resources, plants or animals, and carry health benefits. But the effective ingredient is not identified. Although all of the dietary ingredients in a food product are identified, we do not know which ingredient is effective. If many nutritive, non-nutritive and specific components coexist in a food, their interaction may contribute to promoting health or reducing the risk of disease.[4] Some of them have been sold in the market for more than 10 years and have been presumed safe: agaricus, chlorella, propolis, royal jelly, etc. And it is difficult to distinguish them from the second, third and fourth groups of "health foods."

Changes in Japanese Regulations on "Health Foods"

The concept of functional foods first evolved in Japan in the mid-1980s.[11,12] Japanese food scientists who were members of research teams on functional foods sponsored by the Ministry of Education, Science and Culture, proposed that, while the primary role of food was to provide adequate nutrients to meet metabolic requirements and the secondary role was to provide gustatory and olfactory satisfaction, there existed the tertiary function of promoting a state of well-being and better health and reducing the risk of disease. The scientists defined functional foods as those that emphasized the tertiary element or those that were designed to provide beneficial health effects: enhancement of gastrointestinal functions, immunomodulation, antioxidation, antimutation, antitumor action, hematopoiesis, antithrombogenesis, reduction of blood pressure, blood lipids and blood sugar, neuroregulation, etc. Functional foods can fall into the second, third or fifth group of "health foods" mentioned in the previous section.

The idea of functional foods attracted the great interest of companies in the health food industry, which were looking for products with high added value.[12] Companies in the industry saw a bright future for functional foods and began research and development activities. As the health food market expanded, the former Environment Health Bureau, the Ministry of Health and Welfare, set up the Office of Health Policy on Newly Developed Foods in 1988 and the Advisory Committee on "Functional Foods" in order to build up the regulatory system for "health foods."

A system for "Foods for Special Dietary Uses" had already been enforced under the Nutrition Improvement Act (Health Promotion Act at present). They included food that claimed to be suitable for special dietary uses, e.g., formulated and dried milk for infants, dried milk for pregnant women and lactating mothers, foods for the elderly with masticating or swallowing disorders, and medical foods for the sick. Because the permission of the Ministry of Health was required to market the foods, the Office of Health Policy on Newly Developed Foods decided in 1991 that some of the "health foods" would be categorized as "Foods for Special Dietary Uses" and named "Foods for Specified Health Uses" according to the report of the Advisory Committee of

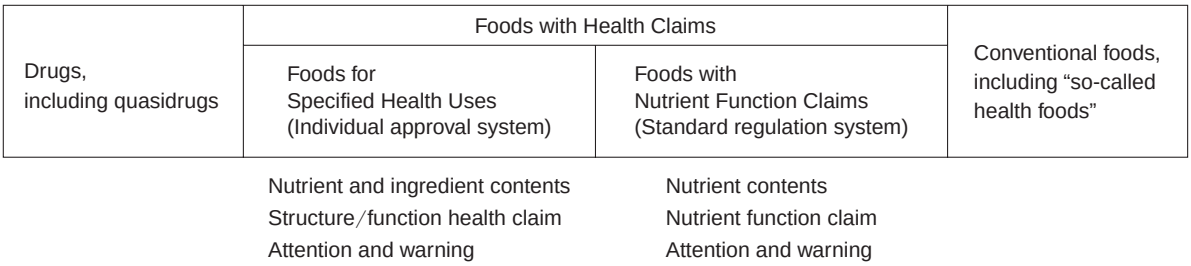


Fig. 1 Current system for regulation of "health foods" in Japan

Functional Foods.[10,13] However, only "health foods" produced in conventional form were included in this category.

Due to the deregulation and opening of the market for foreign products, the Ministry of Health, Labor and Welfare started to revise the guidelines on foods and drug classifications, and to organize an advisory committee for dietary supplements.[13] In March 1995, the following deregulation plan was adopted at a Cabinet meeting: 1) Some vitamins and minerals should be marketed as foods even if they are in the form of tablets or capsules; 2) Some herbs should be recategorized from drugs to foods.

In October 1995, the American Chamber of Commerce in Japan submitted a proposal to market dietary supplements as foods in Japan. In the following year, in March 1996, the Office of Trade and Investment Ombudsman (OTO) decided to open up the market for dietary supplements based on the following: 1) A new category should be set up for dietary supplements; 2) The restrictions on the formulation of dietary supplements should be abolished or largely deregulated; 3) The restrictions on the structure/function claims of dietary supplements should be deregulated.[1,12]

Based on the background described above, the Pharmaceutical and Food Safety Bureau, the Health Ministry, issued notifications and approved the following ingredients as foods, even if they are supplied as tablets and capsules: 13 vitamins in 1997, 8 herbs in 1998, 8 minerals in 1999 and 5 minerals in 2000.[10] In April 2001, a new regulatory system for "health foods," the System of Foods with Health Claims, was enforced in accordance with the reports of two advisory committees on Regulations of Dietary Supplements and Revision of Classification of Drugs and Foods.

System of "Food with Health Claims"

"Foods with Health Claims" are health foods that conform to the safety and efficacy standards set by the Ministry of Health. They consist of two categories: "Foods with Nutrient Function Claims" and "Foods for Specified Health Uses" (Article 5, Enforcement Regulations, Ministerial Ordinance, of Food Sanitation Act, 2001. Fig. 1).

1. "Foods with Nutrient Function Claims"

The Advisory Committee on Regulations of Dietary Supplements (Chairman: H.T.), not only studied nutrients, i.e., vitamins, minerals, amino acids, and fatty acids, but also some herbs or crude drugs, and dietary fibers as candidates ingredients for regulation as dietary supplements.[10,13] Among them, however, the Health Ministry chose only the nutrients and classified them as a new category, i.e., "Foods with Nutrient Function Claims."

"Foods with Nutrient Function Claims" are intended to supplement or complement the daily diet, in cases where the dietary intake is insufficient due to increased age and unhealthy

Table 2 Mandatory Statements on the Label of "Foods with Health Claims" in Japan

"Foods with Nutrient Function Claims"	"Foods for Specified Health Uses"
1. "Food with Health Claim (Food with Nutrient Function Claim)"	1. "Food with Health Claim (Food for Specified Health Use)"
2. Nutrient content Energy, protein, lipid, carbohydrate, sodium, and the mineral or vitamin claimed for function	2. Nutrient content Energy, protein, lipid, carbohydrate, sodium, and the ingredient claimed for function
3. Nutrient function claim	3. Structure/function health claim or enhanced health claim approved
4. Dosage and administration	4. Dosage and administration
5. Method of consumption	5. Method of consumption
6. Percentage of the daily portion of consumption to the recommended dietary allowance	6. Percentage of the daily portion of consumption to the recommended dietary allowance, if RDA is available for the ingredient
7. Attention and warning	7. Attention and warning
8. "Unlike food with specified health uses, this product has not undergone individual evaluation by the Ministry of Health, Labor and Welfare."	

dietary practices or where consumers feel that their diet requires supplementing. At the present time, the definition is the same as that of vitamin and mineral food supplements in the report of the 25th Session of the Codex Committee on Nutrition and Foods for Special Dietary Uses, November 2003,[5] although "Foods with Nutrient Function Claims" can be marketed not only in tablet and capsule form, but also as conventional food, excluding perishable foods.

Twelve vitamins (vitamin A, E, D, B_1, B_2, B_6 and B_{12}, folid acid, niacin, pantothenic acid, biotin, and vitamin C) and two minerals (calcium and iron) were standardized as "Foods with Nutrient Function Claims" in 2001, because the daily requirements for these vitamins and minerals were defined in the sixth revision of the "Recommend Dietary Allowance (RDA) for the Japanese"[14] and the maximum quantities were determined as "over-the-counter" drugs and quasidrugs. In addition, zinc, magnesium and copper were standardized in 2004. The standardization of fatty acids and amino acids is under consideration.

The minimum level of each vitamin or mineral contained in the daily consumption level of "Foods with Nutrient Function Claims" as suggested by the manufacturer should be one-third of the RDA for the Japanese. The maximum level is the same as the maximum amount of nutrient items in "over-the-counter" drugs and quasidrugs.

The eight information statements that are mandatory for "Foods with Nutrient Function Claims" are listed in Table 2.[10,13]

The nutrient content should be stated in accordance with conventional nutrition labeling standards (Notification on Nutrition Labeling Standards, 2001).[10,13] With respect to nutrient function claims, only the statements given in Table 3 are permitted.[10,13]

"Foods with Nutrient Function Claims" do not need to be approved by the Ministry of Health before they are marketed. The manufacturers do not need to register their products with the Ministry of Health before producing or selling them.

2. "Foods for Specified Health Uses"

"Foods for Specified Health Uses" are those that contain dietary ingredients that have beneficial effects on the physiological functions of the human body to maintain and promote

Table 3 Nutrient Function Claims, and Attention and Warnings for "Foods with Nutrient Function Claims" in Japan

Nutrient	Approved Statements for Nutrient Function Claims	Attention and Warnings
Vitamin A	Vitamin A is a nutrient that helps in the maintenance of nocturnal visual acuity. Vitamin A is a nutrient that helps to keep skin and mucosa healthy.	Taking large amounts of this product will not cure disease or promote health. The indicated daily intake should be followed. Women who are in the first trimester of pregnancy or desire to become pregnant should not take this product excessively.
Vitamin D	Vitamin D is a nutrient that increases the absorption of calcium in the intestine and helps the formation of bone.	Taking large amounts of this product will not cure disease or promote health. The indicated daily intake should be followed.
Vitamin E	Vitamin E is a nutrient that helps to protect lipids in the body from oxidation by antioxidative activity and to keep cells healthy.	ditto
Vitamin B_1	Vitamin B_1 is a nutrient that helps to produce energy from carbohydrates and to keep skin and mucosa healthy.	ditto
Vitamin B_2	Vitamin B_2 is a nutrient that helps to keep skin and mucosa healthy.	ditto
Niacin	Niacin is a nutrient that helps to keep skin and mucosa healthy.	ditto
Vitamin B_6	Vitamin B_6 is a nutrient that helps to produce energy from protein and to keep skin and mucosa healthy.	ditto
Folic acid	Folic acid is a nutrient that helps red blood cell formation. Folic acid is a nutrient that contributes to the normal growth of the fetus.	ditto Although this product is a nutrient that contributes to the normal growth of the fetus, better development of the fetus will not ensue from taking large amounts.
Vitamin B_{12}	Vitamin B_{12} is a nutrient that helps red blood cell formation.	Taking large amounts of this product will not cure disease or promote health. The indicated daily intake should be followed.
Biotin	Biotin is a nutrient that helps to keep skin and mucosa healthy.	ditto
Pantothenic acid	Pantothenic acid is a nutrient that helps to keep skin and mucosa healthy.	ditto
Vitamin C	Vitamin C is a nutrient that not only helps to keep skin and mucosa healthy but also has an antioxidative activity.	ditto
Calcium	Calcium is a nutrient necessary for the formation of bones and teeth.	ditto
Iron	Iron is a nutrient necessary for the formation of red blood cells.	ditto
Zinc	Zinc is a nutrient necessary to keep the sense of taste normal. Zinc is a nutrient that helps to keep skin and mucosa healthy. Zinc is a nutrient useful for maintaining health by taking part in the metabolism of protein and nucleic acid.	Taking large amounts of this product will not cure disease or promote health. Because excess intake of zinc can inhibit the absorption of copper, excess intake should be avoided. The indicated daily intake should be followed. Infants and children should not take this product.
Copper	Copper is a nutrient that helps red blood cell formation. Copper is a nutrient that helps the normal activity of many enzymes in the body and bone formation.	Taking large amounts of this product will not cure disease or promote health. The indicated daily intake should be followed. Infants and children should not take this product.
Magnesium	Magnesium is a nutrient necessary for the formation of bones and teeth. Magnesium is a nutrient that helps the normal activity of many enzymes in the body and energy production, and it is necessary to keep the blood circulation normal.	Taking large amounts of this product will not cure disease or promote health. Loose stool or diarrhea can occur by taking large amounts. The indicated daily intake should be followed. Infants and children should not take this product.

Beta-carotene, a precursor of vitamin A, is allowed to state the same nutrient function claims as vitamin A. In this case, the following statement is not required: "Women who are in the first trimester of pregnancy or desire to become pregnant should not take this product excessively."

health and to improve specific health-related conditions (Article 12, Enforcement Regulations, Ministerial Ordinance, of Health Promotion Act, 2003. Article 5, Enforcement Regulations of Food Sanitation Act, 2001.[10,13]). In 1991, when the regulatory system for "Foods for Specified Health Uses" started, they were in conventional food form or processed foods. In 2001, however, the regulatory range was broadened to include capsules, tablets, etc.

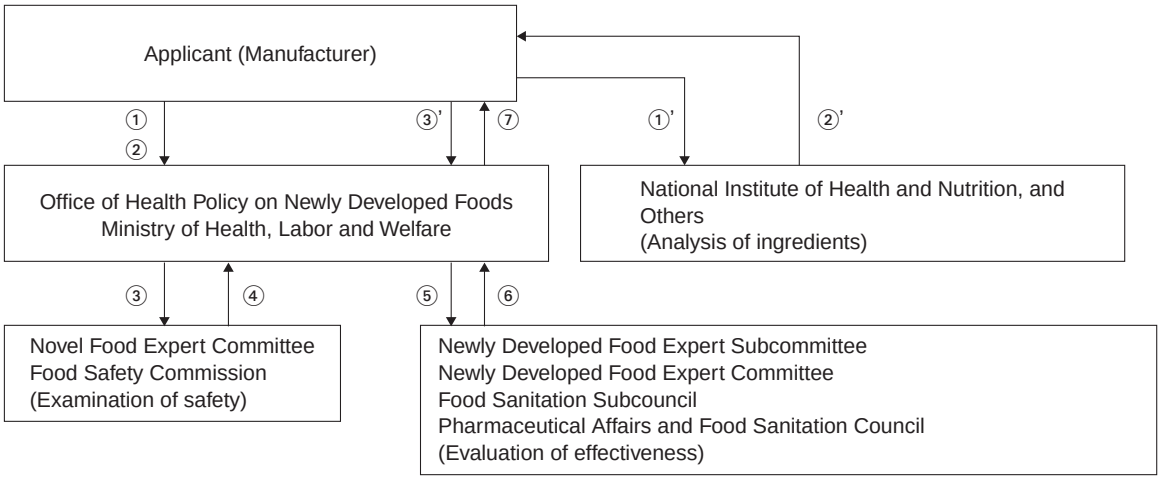
The seven information statements that are mandatory for "Foods for Specified Health Uses" are shown in Table 2. Health claims correspond to the Enhanced (or other) Function Claims of the Codex Alimentarius[5] or Structure/Function Claims of the US.[2] The statements must be based on current relevant scientific substantiation, but they cannot state that a "food for specified health use" can be used to diagnose, prevent, treat, or cure a specific disease. The Council of Pharmaceutical Affairs and Food Sanitation indicated the appropriate health claims as follows.[10]

1) Because Food X contains substance A, Food X may maintain or improve a physiological condition marker that can be easily measured. The marker must be one that people can evaluate by themselves or that is measured in a screening test.
   Statements that are allowed are:
   "Food X helps maintain blood pressure (blood sugar, triglycerides or cholesterol) at normal levels."
   "Food X accelerates the breakdown of body fat."
   A statement that is prohibited is:
   "Food X improves hypertension."
2) Food X may maintain or improve physiological and tissue functions of the human body.
   Statements that are allowed are:
   "Food X improves bowel movements."
   "Food X increases the absorption of calcium."
   Statements that are prohibited are:
   "Food X is effective for detoxification."
   "Food X is effective for activation of lipid metabolism."
3) Food X may improve subjective and temporary physical disorders, but not those that are persistent or chronic.
   Statements that are allowed are:
   "Food X is good or useful for persons who feel physical fatigue."
   A statement that is prohibited is:
   "Food X helps prevent aging."

Claims of reduced disease risk are not allowed for "Foods for Specified Health Uses" in Japan. Since claims of reduced disease risk as defined by the Codex Alimentarius[5] are difficult to distinguish from medical claims, further consideration is necessary to approve the claims for "Foods for Specified Health Uses." From the viewpoint of preventive medicine, "reduced cancer risk through dietary improvement" and "control of hypertension, hyperlipidemia, abnormal glucose tolerance etc. through lifestyle modifications" are the primary prevention of chronic non-communicable diseases.[1] In Japan as in other countries, the Pharmaceutical Affairs Act prohibits the use of terms such as disease, prevention, treatment, cure, and diagnosis for food products. As mentioned above, the statement, "Food X improves hypertension," is a claim of reduced disease risk using the disease name, "hypertension." Therefore, this statement is not permitted in Japan. Statements such as "food X is good for persons whose blood pressure tends to be a little high" and "food X is good for persons who are concerned about their blood pressure," are acceptable.[1,10] Some members of the Advisory Committee on Regulations of Dietary Supplements said that such claims on "Foods for Specified Health Uses" were the same as disease risk reduction claims.[1]

Application for "Foods for Specified Health Uses"

In order to market a product as a "Food for Specified Health Use," the manufacturer is required to submit two documents to the Office



① Two documents, "Application for Labeling Approval" and "Application for Judgment on the Safety and Effectiveness of the Food", are sent to the Office of Health Policy on Newly Developed Foods through Public Health Center and Prefecture or Major City Designated by Government Ordinance or Tokyo Metropolitan Ward.
② The Office checks the two documents before receiving them officially.
③ The Office asks the Novel Food Expert Committee to examine the safety.
④ The Committee notifies the safety confirmation to the Office.
⑤ The Office consults the Newly Developed Food Expert Subcommittee and three others to evaluate the effectiveness and safety of the candidate product. The subcommittee or the Office conducts hearing from the manufacturer, if necessary.
⑥ The Pharmaceutical Affairs and Food Sanitation Council submits the report to the Office.
⑦ The Ministry of Health, Labor and Welfare approves the product as a "Food for Specific Health Use", after confirming the analytical findings of the physiologically active ingredient and nutrients which are measured by the National Institute of Health and Nutrition or another laboratory.

Fig. 2 Flow from application to approval for "Food for Specified Health Use"

of Health Policy on Newly Developed Foods, the Ministry of Health, Labor, and Welfare (① and ② in Fig. 2): "Application for Labeling Approval" under the Health Promotion Act, and "Application for Judgment on the Safety and Effectiveness of the Food" under the Regulatory Standards for Foods, Food Additives, etc. (Ministerial Ordinance).[10,13] First, the Novel Food Expert Committee, Food Safety Commission, the Cabinet Office, examines product safety (③ and ④ in Fig. 2).

Secondly, the Newly Developed Food Expert Subcommittee, the Newly Developed Food Expert Committee, the Food Sanitation Subcouncil, and the Pharmaceutical Affairs and Food Sanitation Council, in this order, evaluate product effectiveness (⑤ and ⑥ in Fig. 2). The Newly Developed Food Expert Subcommittee strictly and impartially decides whether the product should be accepted as a "Food for Specified Health Use." In addition, the National Institute of Health and Nutrition or another laboratory authorized by the Health Ministry determines the contents of the effective ingredient in the candidate food (①', ②' and ③'

Fig. 3 Mark of "Food for Specified Health Use"

Table 4 Foods for Specified Health Use, Japan (March 2004)

Approved Use for····	Biologically Active Component	Product No.	%	Effectiveness[15]	Safety[15]
Bowel movement	Dietary fiber	74	17.5		
	Indigestible dextrin	37		(1)	(1)
	Blond psyllium husk	19		effective	likely safe
	Others	18			
	Oligosaccharide	62	14.6		
	Lactosucrose	28		(2)	(2)
	Others	34			
	Probiotics	62	14.6		
	Lactobacillus	44		likely effective	likely safe
	Bifidobacterium	15		possibly effective	possibly safe
	Others	3			
	Subtotal	198	46.7%		
Serum cholesterol	Dietary fiber	36	8.5		
	Low molecular sodium alginate	16		Algin: possibly effective	Algin: likely safe
	Blond psyllium husk	12		likely effective	likely safe
	Others	8			
	Soy Protein	18	4.2	likely effective	likely safe
	Phytosterol	4	0.9	Beta-sitosterol: likely effective	Beta-sitosterol: likely safe
	Phytostanol	1	0.2	Sitostanol: likely effective	Sitostanol: likely safe
	Others	2	0.5		
	Subtotal	61	14.1%		
Serum triglyceride, Body fat	Diacylglycerol	10	2.4	—	—
	Others	7	1.7		
	Subtotal	17	4.0%		
Blood glucose	Dietary fiber	44	10.4		
	Indigestible dextrin	43		(3)	(3)
	Others	1			
	Others	9	2.1		
	Subtotal	53	12.5%		
Blood pressure	Sardine peptide (Valyl-tyrosine)	22	5.2	—	—
	Oligopeptide from dried bonito	6	1.4	—	—
	Lacto-tripeptide	3	0.7	—	—
	Others	8	1.9		
	Subtotal	39	9.2%		
Dental Health	Sugar alcohol	18	4.2		
	Xylitol	13		likely effective	possibly safe
	Others	5			
	Casein phosphopeptide -Amorphous calcium phosphate*	8	1.9	—	—
	Others	4	0.9		
	Subtotal	30	7.3%		
Bone health	Soy isoflavone	7	1.7	possibly effective	possibly safe
	Others	5	1.2		
	Subtotal	12	2.8%		
Mineral absorption	Calcium				
	Casein phosphopeptide	3	0.7	—	—
	Calcium citrate malate	2	0.5	likely effective	likely safe
	Others	1	0.2		
	Iron				
	heme iron	4	0.9	effective	likely safe
	Others	4	0.9		
	Subtotal	14	3.2%		
Total		424	100%		

Fourteen of 424 products have just been approved by the Newly Developed Food Expert Committee, but not by the Ministry of Health, Labor and Welfare (http://www.mhlw.go.jp/topics/0102/tp0221-2.html).

(1) Although "indigestible dextrin" does not appear in the Natural Medicines Comprehensive Database,[15] it is considered to be likely effective and likely safe based on the description of other dietary fibers.

(2) "Lactosucrose" is considered to be possibly safe based on the description of "fructo-oligosaccharides." Although fructo-oligosaccharide may relieve constipation, more evidence is needed to rate it for this use.

(3) "Indigestible dextrin" is considered to be possibly effective and likely safe.

—: There is no description of the ingredient or its related component.

*: "Calcium phosphate" is effective and likely safe.

in Fig. 2). After the final evaluation by the Pharmaceutical Affairs and Food Sanitation Council, the Ministry of Health officially approves the manufacturer's enhanced function claim and the marking (Fig. 3) on the product (⑥ and ⑦ in Fig. 2).

Effectiveness and Safety of "Foods for Specified Health Uses"

The manufacturer who applies to the government for approval as "Food for Specified Health Uses" for its product must tabulate both published literatures and unpublished or internal office reports on the effectiveness of the product and/or its ingredients, and provide a summary of each literature or report.[10,13] The table must include *in vitro* metabolic and biochemical studies, *in vivo* studies, and human randomized controlled trials (RCT). At the least, one RCT is required and should appear in a journal with a peer review system. Furthermore, the identification of the single, specific active ingredient of the product is required, and the exact mechanism of action should be clarified.

Table 4 shows the effectiveness and safety of the major "Foods for Specified Health Uses" according to the Natural Medicines Comprehensive Database.[15] Most of the products are possibly or likely to be effective and safe. However, the products or their physiologically active components, which were first manufactured in Japan, e.g., indigestible dextrin, lactosucrose, sardine, dried bonito and lactopeptides (which may inhibit the activity of angiotensin converting enzyme), and casein phosphopeptide, are not listed in the database.[15] According to international standards, they will be rated as having insufficient reliable information about its effectiveness and safety. On the other hand, calcium and iron products should be moved from the "Foods for Specified Health Uses" to "Foods with Nutrient Function Claims."

In contrast to dietary supplements in the US,[2] the "Foods for Specified Health Uses" in tablet or capsule form are less than 1%, and almost all of them are found in the form of conventional foods: 35% for beverages, 19% for fermented milk and 13% for confectionery.

Some Issues under Discussion

The Advisory Committee of the New System for Regulation of "Health Foods" (Chairman: H.T.) was set up in April 2003, and submitted an amendment of the regulatory system to the government in June 2004. Some issues proposed by the Committee are as follows.[16]

1) Establishment of the New Regulatory Act

"Health foods" are regulated by several acts, including the Health Promotion Act, Food Sanitation Act and Pharmaceutical Affairs Act. Health food manufacturers and their associations were demanding the regulation of "health foods" under a single act. There are many "health foods" that have been used for more than ten years, and, therefore, they are considered to be safe: royal jelly, propolis, agaricus, spirulina etc. Some of them are of good quality under the Good Manufacturing Practice (GMP). The manufacturers also demanded that quality products be authorized under the new act. However, consumer organizations, the Japan Medical Association and other professional societies were opposed to the plan because more evidence was needed to rate the effectiveness of the products. Thus, the Advisory Committee could not obtain the consensus of the members on the new act.

2) "Foods with Nutrient Function Claims"

As mentioned earlier, 12 vitamins and five minerals were standardized as "Foods with Nutrient Function Claims" as of March 2004. The health food manufacturers claimed that vitamin K, manganese, selenium, chromium, molybdenum and other minerals whose dietary reference intakes were determined in the current RDA for Japanese[14] should be standardized.

The daily intake of minerals cannot be estimated due to the lack of Japanese Food Composition Table[17] for these minerals. Therefore, it is difficult to assess whether a consumer meets the requirements for the minerals, and it is also difficult to set the maximum amount of intake from the supplement. Thus, the Committee did not standardize the vitamin and minerals for "Foods with Nutrient Function Claims."

Suppose that an extract contains substance A which may reduce the risk of osteoporosis, but which is not approved as a "Food for Specific Health Use." The manufacturer enriches the extract with one to two vitamins (e.g., vitamin D) or minerals (e.g., calcium), and labels it "Food with Nutrient Function Claim." Althouth the labeling is not currently illegal, the labeling is misleading. Consumers may be led to believe that the extract or substance A itself is authorized as the "Food with Nutrient Function Claim." Thus, consumer organizations say that the government must prohibit the sales under the new regulatory act. In March 2004, the Office of Health Policy on Newly Developed Foods, the Ministry of Health, warned health food manufacturers that they should enforce the autonomous regulation for labeling more severely, as the number of such products increased. Later, the Advisory Committee decided to prohibit the labeling on the foods.

3) "Foods for Specified Health Uses"

When the Newly Developed Food Expert Subcommittee evaluates the effectiveness and safety of a candidate for "Food for Specified Health Use," the rating method is not always clarified, although it is evidence-based. Both manufacturers and consumers say that the practical ratings should be standardized.

For many "health foods," there has been little scientific inquiry into the active ingredients and the exact mechanism of action.[14] Most "health foods" are a combination of many ingredients. It is quite possible that "health foods" work through the combined effects of multiple ingredients, which means the approach of identifying a single, specific active ingredient is flawed. Thus, the Advisory Committee decided to exempt the manufacturer from submitting data on the action mechanism for a candidate product for "Food for Specified Health Use."

Because a re-evaluation system after marketing "Foods for Specified Health Uses" has not been established, consumers, physicians, pharmacists and dieticians expect to have a system that will monitor the effectiveness and stop the sales of ineffective products.

Health food manufacturers have asked the government to allow the disease risk reduction claims on "Foods for Specified Health Uses." The government intends to allow this in line with the Codex alimentarius, the US and others. However, the Japan Medical Association opposes this because physicians are afraid that if a patient who has to take antihypertensive agents uses a "Food for Specified Health Use" with a risk reduction claim instead, his/her blood pressure will not be well-controlled, and the person may suffer a stroke or heart attack. It will be difficult for Japanese consumers to differentiate a food with disease risk reduction claims from a drug that is effective for the same disease.

The proposal of the Advisory Committee reflects a compromise reached by mutual concession. If the scientific evidence supports the relationship between a food or ingredient and a disease or health-related condition, and provides a very high level of confidence in its validity, claims of disease risk reduction will be allowed for the food. The only disease risk reduction claims permitted will be those related to nutrient to disease for the time being. For example, "Calcium may reduce the risk of osteoporosis. Food X is high in calcium." As shown in this example, the claim must consist of two parts[5]:

(1) Information on an accepted diet-health relationship, followed by
(2) information on the composition of the

product relevant to the relationship.

According to the proposal of the Advisory Committee, the Office of Health Policy on Newly Developed Foods may classify "Foods for Specified Health Uses" into three groups. The first group mainly consists of prebiotics and probiotics. Because they make up almost half of the "Foods for Specified Health Uses," and are likely to be rated as safe and effective, they can be easily standardized and named "Foods for Specified Health Uses under Standard Regulation System." The others may be divided into two on the basis of the strength of the evidence behind the structure/function claims or enhanced function claims. Foods with definite or probable effectiveness based on randomized controlled trials will be simply called "Foods for Specified Health Uses" under the current regulatory process. If the evidence for the claims is tested by studies with a relatively low rating for design (cohort studies, nonrandomized intervention trials with concurrent or historical controls, and case-control studies), the foods, the third group, will be called "Foods for Specified Health Uses with Qualified Structure/function Claims." Therefore, they will be required to carry a disclaimer (i.e., the evidence is limited and not conclusive) like dietary supplements of the third level or C category in the qualified health claims of the United States.[2] However, an evidence-based ranking system for scientific data will be discussed and determined by a group of experts.

4) Health Food Professionals

"Health foods" fall somewhere between conventional foods and drugs, but the boundary between health and conventional foods or between health foods and drugs is not clear. Dieticians deal with conventional foods and pharmacists with drugs. Therefore, "health food" professionals that could provide consumers with the correct information are needed in Japan. The government entrusts the training or education of these professionals to the private sector, but does not grant them national certification.[18]

5) Risk Communication

The National Institute of Health and Nutrition is creating a database of evidence-based information on the effectiveness, safety, interactions with drugs and others, etc. of "health foods" that are manufactured and marketed mainly in Japan.[19] Users will be able to access the database on the Internet, free of charge, from July 2004.

Many "health foods" that are unknown even to specialists are marketed at shops, mail-ordered, sold door-to-door and imported privately using the Internet in Japan. Some of them may carry illegal health claims, and others may contain harmful medicinal or chemical ingredients. More priority should be given to safety rather than effectiveness. The National Institute of Health and Nutrition[19] is operating a network center to gather reports from monitors on the adverse effects of "health foods." The number of monitors is approximately 1,500 (as of May 2004), most of whom are dieticians and pharmacists. If several cases with a specific adverse effect are reported to the center, the cause or the "health food" can be easily identified. The information is then reported to consumers through the monitors. Thus, it is expected that the system will prevent a large-scale epidemic.

Conclusion

The current Japanese system for regulation of "health foods," called "Foods with Health Claims," consists of two categories: "Foods with Nutrient Function Claims" and "Foods for Specified Health Uses."

The label "Food with Nutrient Function Claim" can be freely used if a product satisfies the standard for the minimum and maximum levels for daily consumption. The minimum level should be one-third of the Japanese recommended dietary allowance for each vitamin or mineral. The maximum level is set as the

maximum amount of nutrients in quasidrugs. Twelve vitamins (vitamins A, E, D, B_1, B_2, B_6 and B_{12}, folic acid, niacin, pantothenic acid, biotin and vitamin C) and five minerals (calcium, magnesium, zinc, iron and copper) are currently standardized (as of April 2004).

"Foods for Specified Health Uses" are those that contain dietary ingredients that have beneficial effects on physiological functions of the human body so as to maintain and promote health and to improve health-related conditions. Health claims for these foods correspond to the enhanced or "other" function claims of the Codex Alimentarius or structure/function claims in the US. However, disease risk reduction claims are not allowed. The Ministry of Health, Labor and Welfare gives official approval on a case by case basis allowing the manufacturer to carry the claim and mark on the product, after the Food Safety Commission examines the safety of the product and the Pharmaceutical Affairs and Food Sanitation Council evaluates the effectiveness. The number of "Foods for Specified Health Uses" was 424 as of March 2004, and 65% of them are probiotics or prebiotics.

One reason for the establishment of the system is to provide consumers with the necessary information to choose a good product from numerous health foods. In order to make the system beneficial for consumers, it is very important to train experts who are able to educate, teach, and give advice about "health foods."

In order to maintain and improve people's health and to prevent chronic non-communicable diseases, a key element is a balanced diet of staple foods (e.g., steamed rice), main dishes (fish, meat, chicken, eggs, tofu etc.), and side dishes (vegetables etc.). Healthy individuals should obtain all necessary energy, nutrients and non-nutritious components from regular meals. They should never take quasidrugs containing vitamins and minerals and "health foods," including "Foods with Health Claims," in place of the daily diet and regular meals.

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