Review on Internal Medicine, 1974-Hematology. Concluding Remarks

Gyoichi WAKISAKA

Prof. of the First Division, Department of Internal Medicine,
Faculty of Medicine, Kyoto University

With the recent advance of biochemistry, physics, biology and immunology, there has been great progress not only in the diagnosis and treatment of blood diseases but also in the elucidation of their pathogenesis. In the present symposium, organized and chaired by Dr. Kiyoshi Hiraki, Professor of Medicine, Okayama University School of Medicine, recent developments and future prospects of important problems in hematology were discussed by leading hematologists in Japan.

Dr. Iwasaki reported about aplastic anemia based on his own experience and statistical investigations. Since the pioneer work of Dr. Komiya, it is generally accepted that aplastic anemia is more frequently encountered in Japan than in Western countries. The reason why aplastic anemia, especially of the idiopathic type, is rather common in Japan must be searched for in connection with the pathogenesis of the disease. As to the pathogenesis of aplastic anemia, two theories have been proposed, namely, (1) lesion at the level of stem cells, and (2) sinocapillaropathy of the bone marrow.

Dr. Iwasaki studied the function of the thymus and lymphocytes in aplastic anemia and reported that he found a case of pure red cell aplasia, in which an immunological mechanism could be presumed to be responsible for the pathogenesis of the disease. For the treatment of aplastic anemia, steroid hormone, anabolic steroid and blood transfusion are frequently used. Especially the effect of anabolic steroid on aplastic anemia has recently been recognized. However, the mechanism of the action of anabolic steroid—the reason why anabolic steroid is effective in some cases of aplastic anemia and not in others, and the prevention of side effects of this drug, especially liver injury—must be solved in the future.

Dr. Ohta reviewed the recent advances in the treatment of leukemia. Leukemia has been regarded as an incurable disease. By the development of new antileukemic agents and advances in the supportive therapy for infection and bleeding, the life span of patients with leukemia has been prolonged, and although still very small in number, cases of acute leukemia with survival of more than 8 years—or even cases which might be regarded as completely cured—have been reported. It is hoped that the survival of patients with acute leukemia will be further prolonged by the development of new antileukemic agents, improvement of supportive therapy and appropriate methods of administration of antileukemic agents based on the kinetics of leukemic cells as well as the development of immunotherapy.
Dr. Kawai reported about the recent progress in the study of immunoglobulins. Abnormalities of immunoglobulins may be divided into polyclonal hypergammaglobulinemia, monoclonal hypergammaglobulinemia and immunoglobulin deficiency. Dr. Kawai talked about recent developments in the study of cryoglobulinemia, immunoglobulin deficiency and increase of IgE in the plasma. He reported that a small amount of cryoglobulin of mixed type is found frequently in the plasma of patients with collagen disease. He suggested that this might be an immune complex, and might be related to the pathogenesis or result of so-called immune complex disease.

Dr. Takaku talked about recent progress and future prospects in the study of stem cells. There have been many opinions about the origin of blood cells such as unitarism, dualism etc. However, there has been no agreement as to the morphology and characteristic features of stem cells. Recently new techniques have been devised to study the changes of stem cells in the bone marrow of small experimental animals and humans, and knowledge about the kinetics and pathophysiological significance of CFU-S, ERC, CFU-E and CFU-C is accumulating.

Dr. Takaku found in patients with aplastic anemia a decrease of CFU-C and ERC and suggested that in this disease abnormality in the stem cells common to the erythroid and granulocytic series might exist, while in pure red cell aplasia abnormality of the stem cells of the erythroid series might exist, because in this disease the responsiveness of bone marrow cells to erythropoietin was poor but a decrease of CFU could not be found. He also suggested that abnormality at the level of stem cells might be responsible for the pathogenesis of leukemia based on the finding that in acute leukemia CFU-C decreases markedly in relapse and recovers in remission, and leukemic cells inhibit in some way the differentiation and maturation of CFU-C, while ERC is little affected in this disease. He also suggested that in polycythemia vera ERC does not respond to erythropoietin. A colony of erythroblasts can be formed without the addition of erythropoietin, and in remission ERC responds to erythropoietin. From these observations, he suggested that in polycythemia vera there are two kinds of clones, namely the clone of normal stem cells of the erythroid series and the clone of abnormal stem cells. He also found in patients with cyclic neutropenia an abnormality of the humoral factor in the serum which is related to the differentiation of granulocytes. Studies on the kinetics of stem cells are very valuable not only for understanding the pathogenesis of blood diseases but also for establishing appropriate methods of prevention and therapy of blood diseases.

Dr. Abe talked about the recent progress in the pathophysiology, pathogenesis, diagnosis and treatment of defibrination syndrome. As to the pathogenesis of defibrination syndrome or disseminated intravascular coagulation syndrome, he stated that there are two mechanisms, namely, (1) an increase of coagulation activity occurs in the body, and as a result bleeding or thrombosis develops (primary coagulation, secondary fibrinolysis), and (2) first, an increase of fibrinolytic activity occurs in the body for some reason, and as a result an increase of coagulation activity occurs, and after that the same mechanism operates as stated above and causes bleeding or
thrombosis.

Dr. Abe proposed to call these two conditions defibrination syndrome, because they resemble each other in the clinical symptoms and pathogenesis, and it is often not so easy to differentiate these two conditions. In fact the grade and duration of the phase of accelerated coagulation and increased fibrinolysis differ from case to case, and in the case of acute defibrination syndrome the diagnosis is relatively easy, but in subacute or chronic cases the diagnosis is difficult and must be established by examination of various factors related to blood coagulation and fibrinolysis. Recently much effort has been made on biochemical studies of coagulation and fibrinolysis, and now it has become possible to distinguish to some extent between FgDP and FDP from the thermostability of the antigenicity, paracoagulation, reaction to factor XIII and analysis of the subunit. It is important to establish the method of diagnosis of defibrination syndrome in order to evaluate accurately the state and stage of coagulation and fibrinolysis abnormalities and to choose a proper method of treatment of the abnormal conditions.

It is presumed that the defibrination syndrome is closely related with the pathophysiology in malignant tumors, liver diseases, renal disturbances and cerebrovascular injuries. Therefore studies on the treatment of defibrination syndrome are important not only for the symptomatic treatment of bleeding but also for the prophylaxis of these pathological conditions.

Dr. Tsunematsu reported about the clinical aspects and pathogenesis of autoimmune hemolytic anemia based on his own experience and reported cases in the literature. Autoimmune hemolytic anemia may be classified into idiopathic type and secondary type, or warm type and cold type according to the optimal temperature for the antibody. He reported that there is not necessarily a close relationship between the amount of antibody and the grade of hemolysis, and he experienced cases of a positive Coombs’ test without anemia and cases with severe autoimmune hemolytic anemia with a negative Coombs’ test.

He suggested that the hemolysis in autoimmune hemolytic anemia is influenced not only by the amount of antibody, but also by the qualitative difference of antibody, and other factors such as the complement and the function of macrophage and lymphocyte. He demonstrated in patients with autoimmune hemolytic anemia the presence of lymphocytes sensitized with the membrane of red blood cells by a leukocyte immigration inhibition test, using lymphocytes brought in contact with red cell membrane as the antigen. He presumed that in these cases, when the lymphocytes come into contact with an antigen, they produce mediators such as MIF, and cause hemolysis by retaining the macrophage at the affected site and accelerating their phagocytic activity.

The etiology of idiopathic autoimmune hemolytic anemia is unknown, but Dr. Tsunematsu regarded pregnancy, delivery, drugs and heredity as some of the initiating factors for the development or exacerbation of autoimmune hemolytic anemia. These factors are presumed to cause abnormalities of antibody-producing organs and
lead to production of red blood cell antibodies. Autoimmune hemolytic anemia is a model of autoimmune disease, and the elucidation of the etiology and mechanism of development of the disease will make a great contribution towards clarifying the pathogenesis of autoimmune disease.

Before closing the symposium, I would like to express my sincere gratitude to Prof. Hiraki and his associates for their effort in planning and conducting this meeting and to the speakers and chairmen for their cooperation.