new horizons in
RHEUMATOID ARTHRITIS

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New Horizons in Rheumatoid Arthritis

Proceedings of the International Congress on Rheumatoid Arthritis, Hakone, 24–26 August, 1980

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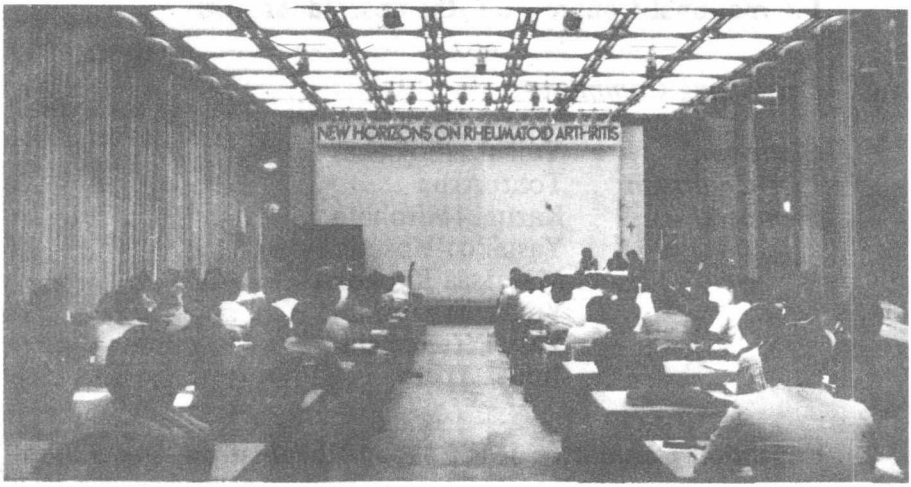

View during the Meeting

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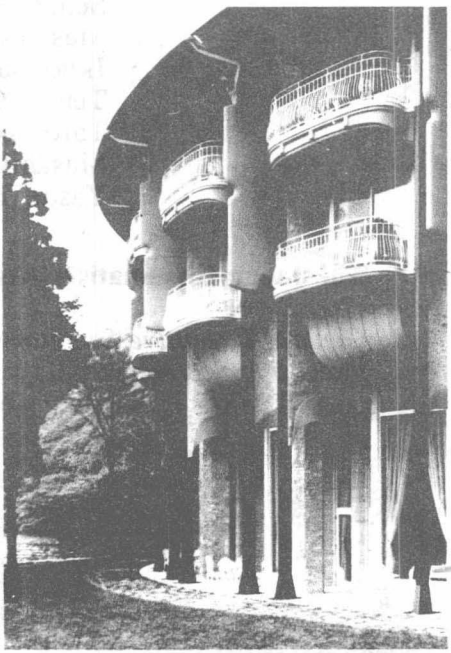

Hakone Prince Hotel, scene of the Meeting

Preface

Rheumatoid arthritis is one of the major hazards for mankind because of the large number of patients suffering from the disease, the severe discomfort caused to patients and the lack of really effective treatment for the disorder.

The etiology of rheumatoid arthritis is still unknown. However, rheumatic diseases have been the subject of intensive investigation recently and as a result, particularly due to the recent progress in immunology, it appears that 3 factors can be implicated in the pathogenesis of rheumatoid arthritis: immunological disturbance, hereditary abnormalities, and infections. It is well known that a variety of antirheumatic drugs has been developed through the efforts of many laboratories in pharmaceutical companies all over the world. Most of them are nonsteroidal anti-inflammatory agents, but some are immunosuppressive and immunomodulating agents which are new and promising chemical compounds for the management of rheumatic diseases. In addition, surgical procedures have become safer and more accessible than before for disabled patients.

We felt that the time had come for a review of the present status of investigations on the etiology, management and other problems in rheumatoid arthritis, to find better ways of management of patients and to establish a new strategy to combat this intractable disorder. In other words, 'New Horizons' have appeared in rheumatoid arthritis.

This is the reason why we decided to hold this International Meeting in Hakone, Japan, inviting rheumatologists and investigators of rheumatology from abroad and throughout Japan.

This meeting was sponsored by the Education Committee of the Japan Rheumatism Association. Our Committee is very active in promoting rheumatology which is a very young field of medicine in this country. The reason for this is that rheumatoid arthritis has been treated more frequently using traditional Japanese medicine such as hot spring baths, massage, acupuncture and moxabustion than by modern means of treatment. In addition, most doctors have paid more attention to malignancies and cerebral strokes which have a high incidence in Japan.

Our Committee has developed an educational system for rheumatology consisting of 3 steps. The first step is for general practitioners, and we hold seminars 3 or 4 times a year in local cities throughout the coun-

try. The second step is for young physicians who intend to become specialists or investigators of rheumatoid diseases, and, for this purpose, we hold a 2-day seminar once a year in Tokyo, Osaka or other big cities in Japan. The third step is to have specialists of rheumatology meet and discuss recent advancements in rheumatology, occasionally inviting foreign guests as in the case of this International Meeting.

I should like to mention the Congress symbol. Although no professional artist, I designed the symbol for this meeting, which you can find all through this book. You can see in it the letter 'R', which symbolizes not only rheumatology, but also a patient suffering from rheumatic disease, squatting and tolerating the pain in the joints and other discomforts. I set this letter against the landscape of Hakone, where this meeting was held. Hakone is one of the most beautiful places in Japan with Lake Ashi in the center and Mount Fuji in the background. When we look at the letter 'R' from a new angle, rheumatology appears to be on the mark ready to set off for new horizons, new progress in rheumatology and better management of patients. This is what I expect from this meeting. I hope that contributions and discussions in this book will be valuable for the future development of rheumatology.

In closing, I wish to express my gratitude to all the participants in this meeting, particularly guests from abroad, for their excellent papers. I am also very thankful for the help and efforts of the members of the Organizing Committee in organizing this International Meeting. Finally, I wish to express my appreciation for the financial support made by the Nippon Merck-Banyu Co., Ltd. towards the publication of these Proceedings.

Yuichi Shiokawa, M.D.
Chairman, Organizing Committee

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RHEUMATOID FACTORS AND OTHER AUTOANTIBODIES IN RHEUMATOID ARTHRITIS

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The most frequently observed autoantibodies in rheumatoid arthritis (RA) are rheumatoid factors (RF) and other anti-Ig antibodies. In addition, anti-nuclear antibodies (ANA) and anti-collagen antibodies are often seen, and there are scattered reports of other autoantibodies reacting with various kinds of cells and molecules.

Anti-Ig antibodies

As shown in Table 1, the anti-Ig antibodies include a number of autoantibodies with specificity for different Ig classes and different determinants on the Ig molecules (6, 15). All of them can be found in sera from patients with RA, but for diagnostic purposes the most important are RF, i.e. the anti-Ig antibodies reacting with the Fc part of IgG. Also within RF various specificities can be found, directed against different IgG subclass determinants and genetic types (15). Among the antibodies to enzyme treated Ig, the most well known is the one reacting with pepsin digested IgG, $F(ab')_2$ IgG, usually called pepsin agglutinator. Pepsin agglutinator can be observed as frequently as RF in RA, but is diagnostically of less importance, since it is frequently observed also in sera from normals. The anti-antibodies are rarely seen, but are of great theoretical interest since they may be directed against idiotypic determinants on anti-Rh antibodies (16).

TABLE 1. Anti-immunoglobulin antibodies.

1.	Rheumatoid factors, reacting with Fc IgG.
2.	Antibodies to the Fc fragment of other Ig classes.
3.	Antibodies to enzyme treated Ig ("enzyme agglutinators").
4.	Anti-antibodies, reacting with the Fab fragment of anti-Rh antibodies.
5.	Antibodies to free Ig light chains.

There is today no doubt that RF behaves like a true autoantibody *in vivo* since both IgM-IgG complexes of high molecular 22S type and IgG-IgG complexes of intermediate

type have been detected in serum (6). The pathogenetic importance of these circulating rheumatoid factor complexes is, however, probably small, since they do not usually bind complement. A possible explanation for this is that they represent selected types of complexes which have not been withheld and trapped in the rheumatoid synovial tissues or joint fluids.

Detection of free, uncomplexed RF in serum is easily done by classical serological technique, but complexed RF frequently escape detection by these methods. There are, however, several methods for detection of both so called hidden IgM and IgG rheumatoid factors (4, 13).

In RA, RF is also found in joint fluid and rheumatoid synovial tissue. In the synovial fluids there is an inverse relationship between IgG complexes containing RF and complement levels (19). The titers of RF in synovial fluids are usually identical to or somewhat lower than those in the corresponding sera. In a few cases the titer in synovial fluid is higher than in serum, suggesting a local production of RF in the joint (5). A more direct demonstration of RF production in plasma cells in the synovial tissue is performed with immunofluorescence technique, demonstrating binding of FITC-labelled aggregated IgG to cytoplasma of plasma cells (12). Such studies, and studies on eluates from synovial tissues, also demonstrated extracellular IgG complexes containing both IgM and IgG rheumatoid factor (12, 13). The IgG RF-containing complexes were detected in both sero-positive and sero-negative patients with active disease and were demonstrated after pepsin splitting of the Ig complexes (13, 14).

Local production of IgM RF in rheumatoid synovial tissue has further been demonstrated by a hemolytic plaque technique (18), by incubation of mononuclear cells eluted from synovial tissues in a gel with complement and red cells sensitized with rabbit IgG. By this technique, a considerable proportion of the mononuclear cells in the synovial tissue of sero-positive patients demonstrated IgM RF production (Table 2).

TABLE 2. Detection of rheumatoid factor plaque-forming cells (RF-PFC) in cell suspensions eluted from rheumatoid synovial tissue. (Data from[18]).

Waaler-Rose titer in serum	Number of patients	Number of RF-PFC/10^6 synovial tissue cells
< 16	11	0 (10 patients) 130 (1 patient)
64-128	4	136-964
256-512	5	11-3958
1024	4	432-17,245

Anti-nuclear antibodies

By indirect immunofluorescence test (ANF-test) anti-nuclear antibodies (ANA) can be demonstrated in sera from patients with RA in 20-40%. The immunofluorescence pattern is usually homogeneous, indicating a specificity for the DNA-histone complex. The possible pathogenetic importance of ANA in RA is still unclear, and there is no clear demonstration of production of ANA in plasma cells in the rheumatoid synovial tissue or disposition of ANA in IgG-complexes in this tissue.

Recently, much attention has been drawn to the observation that sera from RA patients contained an antibody to Epstein-Barr virus (EBV) associated antigen, which appears in the nuclei of transformed B-cells several weeks after in vitro EBV infection (1). This antigen was consequently designated rheumatoid arthritis nuclear antigen (RANA). The antibody to this antigen is probably different from the usual antibodies to the Epstein-Barr nuclear antigen (EBNA) which appears earlier in transformed B-cells. Later studies have, however, demonstrated that anti-RANA antibodies are present in a large proportion of sera from normal individuals and can be clearly ascribed to prior infection with EBV (3). Anti-RANA antibodies are therefore not specific for RF and cannot be taken as evidence for EBV infection as an etiologic factor in RA.

Anti-collagen antibodies

In sera from patients with RA, the antibodies to human collagen can be demonstrated in up to 40% (17). Since intracytoplasmic inclusion of collagen in synovial fluid cells has also been demonstrated, the possibility exists that immune complexes with collagens are of pathogenetic importance in RA.

Other autoantibodies in RA

It has recently been demonstrated that in some cases of sero-negative RA, antibodies to smooth muscle antigens are present both in serum and synovial fluid (8). In some of these cases, the titers indicated that these antibodies were produced locally in the joint. The interpretation of this observation is still unclear, but since antibodies to smooth muscle antigens are known to occur in many types of virus diseases, it might be consistent with the hypothesis that viruses are present in the rheumatoid synovial tissue.

It was recently also reported that anti-thyreoglobulin antibodies were frequently present in rheumatoid synovial fluids and not in the corresponding sera, and this was again taken as evidence for a local production of these auto-antibodies in rheumatoid joints (2). However,

later reports (7, 10) indicate that this observation was due to technical factors causing false positive tests for anti-thyreoglobulin in the synovial fluids.

Immunoconglutinin, which is an auto-antibody to activated complement factor C3, have been demonstrated in eluates from rheumatoid synovial fluids (9). Since this antibody can enhance the fixation and activation of complement by immunecomplexes in vitro, it may be of pathogenetic importance in RA.

Why are all these autoantibodies produced in RA?

As for autoantibodies in general, the stimulus for production of these antibodies in RA is largely unknown. However, from studies both in man and animals, it is clear that the production of RF may at least partly be considered as a normal antibody response to Ig bound in immunecomplexes or altered in other ways in vivo (15). This "altered antigen" mechanism may be the stimulus also for the other autoantibodies in RA, but some recent observations indicate that an unspecific increase B-cell activity may play a role. Firstly, in some cases of sero-negative RA, an oligoclonal local production in the joint of antibodies to several viruses and bacteria can be demonstrated at the same time in one joint (11). It seems unlikely that this is caused by specific stimulation in all cases. It appears more likely that these antibodies, and possibly some of the autoantibodies described above, are results of a general B-cell activation, or that there is one specific antigenic stimulation causing co-activation of many other B-cell clones in the joint. If a generally increased B-cell activity is present, this may theoretically either be due to an abnormality in the B-cells or to an abnormal regulation by the T-cells. As described in the chapter on suppressor cell activity in patients with rheumatoid arthritis in this book (see Førre et al), there is evidence for a diminished suppressor cell activity locally in the joint in RA. Future work should therefore include studies on the fine functions of the cells involved in the immune responses in the rheumatoid synovial tissue, to see whether the autoantibodies produced can be explained by an abnormal function of these cells, or if the autoantibodies result from a quantitatively or quantitatively abnormal antigenic stimulus.

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