

new horizons in
RHEUMATOID
ARTHRITIS

Editors
Yuichi Shiokawa
Tohru Abe
Yasuo Yamauchi

New Horizons in Rheumatoid Arthritis

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



Editors

YUICHI SHIOKAWA

Department of Rheumatology
Juntendo University School of Medicine
Tokyo

TOHRU ABE

Department of Internal Medicine
School of Medicine, Keio University
Tokyo

YASUO YAMAUCHI

Department of Orthopaedic Surgery
Juntendo University School of Medicine
Tokyo



1981

EXCERPTA MEDICA, AMSTERDAM-OXFORD-PRINCETON

© Excerpta Medica 1981

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without permission in writing from the publisher.

International Congress Series No. 535
ISBN Excerpta Medica 90 219 0460 8
ISBN Elsevier North-Holland 0 444 90185 x

Library of Congress Card Number 81-3178

Publisher:

Excerpta Medica
305 Keizersgracht
1000 BC Amsterdam
P.O. Box 1126

Sole distributors for the USA and Canada:

Elsevier North-Holland Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

Printed in The Netherlands by Groen, IJmuiden

International Congress on Rheumatoid Arthritis

Organizing Committee

<i>Chairman</i>	Yuichi Shiokawa
<i>Vice-Chairman</i>	Tohru Abe
<i>Members</i>	Kazushi Hirohata
	Yasuhiro Hosoda
	Masahisa Kyogoku
	Yutaka Mizushima
	Yasuo Yamauchi
	Junichi Yata

Education Committee of the Japan Rheumatism Association

<i>Chairman</i>	Yuichi Shiokawa
<i>Vice-Chairman</i>	Tohru Abe
<i>Members</i>	Takeshi Azuma
	Kazushi Hirohata
	Seiichi Kawakita
	Masahisa Kyogoku
	Ikuo Nagaya
	Teiichi Oda
	Taro Okazaki
	Masahiko Okuni
	Yasuo Yamauchi

The Japan Rheumatism Association

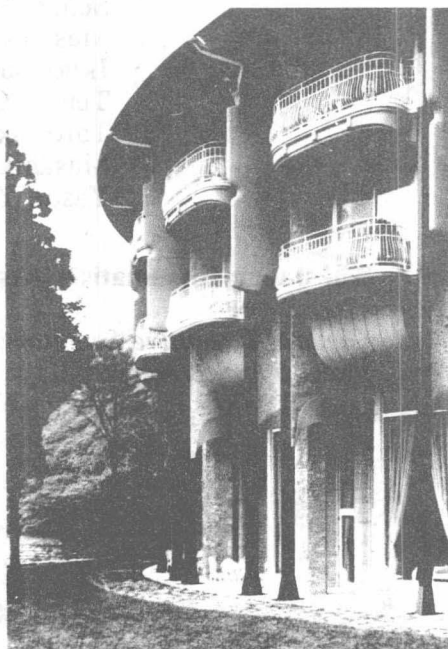
<i>General Executive Secretary</i>	Yoshio Oshima
<i>Executive Secretary</i>	Kazushi Hirohata
	Takamasa Kageyama
	Masataka Katsu
	Yuichi Otaka
	Satoshi Sasaki
	Kanji Shichikawa
	Yuichi Shiokawa
	Takashi Sugiyama
	Tamotsu Terawaki
<i>Secretary</i>	Takayoshi Koketsu



View during the Meeting



Chairman: Yuichi SHIOHARA, M.D.



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 non-steroidal 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

Contents

Preface

vii

I. RHEUMATOID FACTORS AND OTHER AUTOANTIBODIES

Rheumatoid factors and other autoantibodies in rheumatoid arthritis <i>J.B. Natvig and O.J. Mellbye</i>	3
Characterization of rheumatoid factors with a shared idiotypic that react with DNA-histone and description of their occurrence in the rheumatic disease <i>V. Agnello</i>	8
The diagnostic significance of IgG rheumatoid factors and anti-peri-nuclear factors <i>T.E.W. Feltkamp, N.G. Verwey-Burke and A.E. Schipper</i>	16
Quantitation of complex and free rheumatoid factor in each immunoglobulin class by absorption of Fc-receptor bearing cells <i>T. Suzuta and K. Shimo</i>	22
Influences of rheumatoid factors on solubilization of immune complex due to complement <i>S. Hirose and Y. Yukiya</i>	29
Detection of IgE and IgG rheumatoid factors by ELISA and their clinical significance <i>Y. Mizushima, K. Hoshi, Y. Shoji, H. Takahashi and T. Ogita</i>	37
Antibodies to extractable nuclear antigens (ENA): Significance and usefulness in diagnosis <i>F.C. McDuffie</i>	46
Antibodies to nuclear acid protein antigens (NAPA) in patients with systemic rheumatic diseases <i>N. Kurata, S. Miyawaki and T. Ofuji</i>	53
Chairman's Remarks <i>T. Suzuta, M. Mannik and Y. Mizushima</i>	59

II. IMMUNE COMPLEXES

Section 1

Detection and significance of immune complexes in rheumatic disease <i>M. Mannik and A.O. Haakenstad</i>	63
---	----

Detection and partial characterization of immune complexes and other substances in certain rheumatic diseases using monoclonal rheumatoid factor reagent <i>V. Agnello, G. Ibanez de Kasep and T. Mitamura</i>	71
Detection and characterization of circulating immune complexes in rheumatic diseases by solid phase C1q <i>R. Kasukawa, S. Suzuki and M. Sato</i>	76
Immune complex detection in rheumatic fever and in juvenile rheumatoid arthritis <i>Y. Hamashima and K. Kawakami</i>	83
Detection and characterization of circulating immune complexes by human red blood cell (HRBC) radioimmunoassay <i>T. Aikawa, K. Tanimoto and Y. Horiuchi</i>	89
Chairman's Remarks <i>Y. Hamashima and V. Agnello</i>	94

Section 2

Role of retroviral gp70 immune complexes in the pathogenesis of murine lupus nephritis <i>S. Izui, V.E. Kelley, P.J. McConahey and F.J. Dixon</i>	96
Polyclonal B cell activation and autoimmunity in New Zealand mice: Anti-DNA antibodies and proteinuria <i>S. Hirose, H. Yoshida, K. Ohta, Y. Nakai, N. Maruyama and T. Shirai</i>	102
Role of immune complex in the pathogenesis of arteritis in SL/Ni mice: Possible effect as accelerator rather than initiator <i>M. Nose, M. Kawashima, K. Yamamoto, T. Sawai, N. Yaginuma, K. Nagao and M. Kyogoku</i>	109
Spontaneous polyarthritis in MRL/1 mice <i>C. Abe and Y. Shiokawa</i>	116
Self-associating IgG-rheumatoid factors <i>M. Mannik and F.A. Nardella</i>	124
Chairman's Remarks <i>M. Kyogoku and F.C. McDuffie</i>	132

III. CELLULAR IMMUNOLOGY

Section 1

Suppressor cell defects in systemic lupus erythematosus <i>C. Morimoto, E.L. Reinherz and S.F. Schlossman</i>	137
Suppressor cell activity in patients with rheumatoid arthritis <i>Ø.T. Førre, J.B. Natvig, J.H. Dobloug and C. Chattopadhyay</i>	145
Role of suppressor cells in systemic lupus erythematosus <i>T. Sakane and M. Honda</i>	150

Abnormalities of T _g -cells in rheumatoid arthritis <i>J. Tanaka and J. Yata</i>	158
Anti-lymphocyte antibodies in systemic lupus erythematosus <i>T. Toguchi, T. Abe, M. Kiyotaki, C. Morimoto, M. Tomii and M. Homma</i>	168
Interaction of immune complexes and lymphocytes <i>K. Tanimoto, T. Morito, H. Nakai and Y. Horiuchi</i>	178
Cellular aspects of in vitro antibody production to DNA <i>S. Sawada, S. Nishinarita, I. Amaki and N. Talal</i>	183

Section 2

Characterization of the surface phenotype of T cells and lining cells found in the synovial tissues of patients with rheumatoid arthritis <i>G.R. Burmester, A.D. Bona, D.T. Yu, H.G. Kunkel, G. Steiner and R.J. Winchester</i>	189
Chairman's Remarks <i>T. Okazaki, S.F. Schlossman and N. Tsuyama</i>	196

IV. TREATMENT OF RHEUMATOID ARTHRITIS

Treatment of rheumatoid arthritis <i>J. Villiaumey</i>	201
Pros and cons of rheumatoid arthritis surgery <i>P. Raunio</i>	217
Plasma exchange for rheumatoid arthritis using a new bag system (Y-S type) <i>Y. Shiokawa, J. Yamagata, S. Yuasa and K. Shiozawa</i>	222
Recent status of treatment of rheumatoid arthritis in Japan <i>T. Kageyama</i>	231
Chairman's Remarks <i>Y. Yamauchi, P. Raunio and I. Nagaya</i>	235

V. GENETICS

HLA studies in rheumatoid arthritis <i>P. Stastny</i>	239
Japanese rheumatoid arthritis and HLA <i>T. Sasazuki, N. Ohta, Y.K. Nishimura, T. Abe, C. Abe and Y. Shiokawa</i>	247
Chairman's Remarks <i>J. Villiaumey, M. Okuni and S. Kawakita</i>	255

VI. GENERAL DISCUSSION

Chairman's Remarks

K. Shichikawa, Y. Hosoda and T. Azuma

259

VII. POSTER PRESENTATIONS

The results of total joint replacements of the weight bearing joints in rheumatoid arthritis

S. Yoshino

263

Usefulness of cryotherapy as a physiotherapy for rehabilitation of rheumatoid arthritis

N. Nobunaga, T. Todoroki and F. Goto

265

Fate of oral gold in the body

T. Funyu and T. Okazaki

267

CCA, a new immunoregulator, in rheumatoid arthritis: Clinical effect, blood level and influence on immune complex

S. Kosaka

269

Studies of causes of death in autopsied cases with rheumatoid arthritis

Y. Matsuoka, M. Obana, S. Mita, M. Kohno, S. Irimajiri, I. Fujimori and J. Fukuda

271

Arthro-osteitis associated with pustulosis palmaris et plantaris: A new rheumatic disease of seronegative spondylo-arthritis

H. Sonozaki and M. Kawashima

273

Clinical evaluation of circulating immune complex by means of C1q enzyme immunoassay

M. Umeda, T. Okazaki, H. Yamanaka, H. Yagi, M. Okuno, E. Azuma, K. Nishioka, K. Miyaji and T. Mukojima

275

Polymorphonuclear leukocytes have different and specific receptors for several attractants on cell membrane

H. Warabi, Y. Murakami, Y. Shiokawa and E. Schiffman

277

Naturally occurring human antibodies to the F(ab')₂ portion of IgG (anti-Fab) in rheumatological disorders

H. Nasu, C. Abe, Y. Shiokawa, D. Chia and E.V. Barnett

279

Anti-glycolipid autoantibody detected in the sera from SLE patients

T. Hirano, H. Hashimoto, Y. Shiokawa, M. Iwamori, Y. Nagai, M. Kasai, Y. Ochiai and K. Okumura

281

A clinical and pathological study of esophageal lesions in systemic lupus erythematosus

Y. Hosoda, T. Ishii, N. Tominaga and M. Takano

283

Manipulation of anti-DNA antibody in old NZB/W F₁ mice

F. Endo, T. Sasaki, T. Kadono and K. Yoshinaga

285

List of participants

288

Author index

298

Subject index

300

I. RHEUMATOID FACTORS AND OTHER AUTOANTIBODIES

RHEUMATOID FACTORS AND OTHER AUTOANTIBODIES IN RHEUMATOID ARTHRITIS

Jacob B. Natvig and Ove J. Mellbye

Institute of Immunology and Rheumatology, Rikshospitalet, The National Hospital, Oslo, Norway.

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'), 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 cytoplasm 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 from¹⁸).

Waller-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-thyroglobulin 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-thyroglobulin 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 immunocomplexes 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 immune-complexes 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.

REFERENCES

1. Alspaugh, M.A. and Tan, E.M. (1976): Arthritis Rheum. 19, 711.
2. Blake, D.R., McGregor, A.M., Stansfield, E. and Smith, B.R. (1979): Lancet ii, 224.
3. Catalano, M.A., Carson, D.A., Niederman, J.C., Feorino, P. and Vaughan, J.H. (1980): J. clin. Invest. 65, 1238.