Intestinal Mucosal Damage and Repair

5th Eisai Biwako Symposium
November 19–20, 1999, Lake Biwa, Shiga, Japan

Guest Editor
Tadao Bamba, Shiga

71 figures, 8 in color and 10 tables, 2001
Drug Dosage
The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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This symposium has been held once a year for 5 years:
1st Symposium, 27th–28th October, 1995
2nd Symposium, 22nd–23rd November, 1996
3rd Symposium, 14th–15th November, 1997
4th Symposium, 13th–14th November, 1998
5th Symposium, 19th–20th November, 1999

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Preface

The Eisai Biwako Symposium on ‘Intestinal Mucosal Damage and Repair’ was held from 1995 to 1999 at the Hotel Royal Oak in Otsu, the beautiful city located on Lake Biwa, the largest lake in Japan. The most interesting topics are to elucidate the pathophysiology of chronic inflammation in the intestine, which may give us new insights into the treatment of chronic intestinal disorders such as ulcerative colitis and Crohn’s disease.

There are growing impacts of the mucosal immune system and mucosal inflammation on clinical medicine as well as experimental models, due to realization of the fact that the gastrointestinal tract is important as the first defense line of the body against endogenous and exogenous harmful agents such as gastric acids, various digestive enzymes, bacteria and their metabolites, viruses, and food antigens. Recent studies have begun to disclose the changes of chemical mediators and cytokines of chronic inflammation in the intestine. Animal models with the mutant immunologic genes spontaneously develop chronic colitis. But colitis cannot be induced if the animal is reared under germ-free conditions, suggesting that the bacterial flora is necessary for the initiation of chronic colitis. Chronic inflammation in the intestine may be due to an immune dysregulation, which presumably results in an excess immunological reaction against the bacterial flora and/or its metabolites.

In general, epithelial cells must spread in the damaged mucosa and reseal the denuded surfaces rapidly. This process of reestablishment of epithelial continuity is desirable to block fluid and electrolyte loss and to prevent the entrance of various pathological antigens. In this process, various humoral factors such as cytokines mediate cell migration and proliferation. In addition, various metabolites generated by normal flora, such as short-chain fatty acids, also participate in the process of mucosal repair.

It is now believed that the disturbance of mucosal repair is closely associated with the pathogenesis of inflammatory bowel disease, in which the mucosal immune system, including the secretory immunoglobulin system and other cellular responses, plays an important role. In this symposium, many interesting papers of experimental and clinical studies were presented and discussed by basic researchers and gastroenterologists in Japan. Through this symposium many achievements defined the pathophysiology of chronic intestinal mucosal damage and repair, especially the findings of mucosal immunological changes. All papers presented in each symposium have been published in Progress in Medicine, and several presentations have already been published in high-quality journals as original articles. This supplement includes the review articles on the intestinal mucosal immune system and its regulatory mechanisms from experimental and clinical aspects as well as the original papers presented at the symposium. I would like to believe these proceedings to be landmarks for researchers and clinicians in understanding new aspects of their investigations on Gastroenterology.

Finally, the publication of these proceedings was made possible by the kind and valuable assistance of the most outstanding gastroenterologists in Japan, as well as the many efforts on behalf of the Eisai Pharmaceutical Co. Ltd. in Japan and S. Karger publishers in Switzerland.

Tadao Bamba
General Secretary of Biwako Symposium on ‘Intestinal Mucosal Damage and Repair’
Shiga University of Medical Science
I have been very lucky to have had the pleasure to enjoy the beautiful landscapes and the seasonal red autumn leaves around the Lake Biwa as the ‘Biwako (lake Biwa) symposium’ has been held there for the last 5 years. At the time of the symposium, I always left Kyoto Shin-kan-sen station by car for the hotel in Ohtsu, crossing Mt. Ohsaka, and got very excited at the view of Lake Biwa and its surrounding beauty every year.

In these last 5 years, I have been lucky to have been able to enjoy great opportunity and experiences: The happiness of sharing the beautiful red maple autumn leaves around Mt. Takao’s Shingoin Shrine guided by Dr. Shiro Hosada, the symposium chairman and professor emeritus of Shiga Medical University, taking walks to Kinomoto town in Kohoku (on the northern shores of Lake Biwa) through Anegawa, tasting the classical Biwako food, and looking over Mt. Shizugadake and imagining the historical Japanese medieval period. I could enjoy eating the traditional ‘Funazushi’ (carp sushi), which was regarded as a formal dish in northern Kyushu and Ohmi (the present Shiga prefecture including Lake Biwa), according to the ‘Engishiki code’ compiled in the year 927, although one cannot get such an old dish in the present northern Kyushu. I could also enjoy the Chinese ‘Narezushi’ made from carp, and the Biwako carp named ‘rigyo’ often reminded me of ‘a picture of the carp in dream’ beautifully expressed in the ‘Ugetsu Story’, a novel written by an author of the Edo period. In Kohoku, I had the honor of seeing the tremendously wonderful Kannon with eleven faces, the Goddess of Mercy in the Kannon Hall, which was built after the burning down of a famous temple by Nobunaga Oda in the late 16th century. I could visit Ohmi-Hachiman city often and enjoy the riverside district commanding ‘Nishi-no-Umi’ (Western sea) with touches of the origin of the old Japanese ‘Ohmi merchants’, and was fortunate enough to be able to visit the William Merrell Vories Commemorative Hospital twice.

All these happy memories were made possible by the fact that the Royal Oak Hotel in Kayanoura, Ohtsu City was selected as the venue for the symposia. In this sense, I would like to give my appreciation to Eizai Co. Ltd., who sponsored the symposium as well as its related people.

The symposium, which started every year on a Friday afternoon, was, in my opinion, very attractively presented and professional. As soon as a social gathering ended, a heated night session took place continuing late into the night. On Saturday, the morning session of the symposium started at 9 o’clock and the discussion was always wrapped up with good results and the resolution and expectations of meeting the participants again at the same place in the next year.

Thus, since the first symposium in October 1995, participants have been seriously exchanging information and discussing ‘Intestinal Mucosal Damage and Repair’ every year, and the result of this has been the continuation of the up to now 5th symposium in November 1999. These 5 years happened to fall in the time when Japanese clinical and experimental research had come to a halt after the implementation of a new Good Clinical Practice code, and when not many research meetings were being held under the auspices of pharmaceutical companies. In other words, it was a time when many clinical researchers were discouraged from participating in such meetings, as the symposium organizers and pharmaceutical companies had lost
their positive outlook toward medical development. In spite of this, these symposia were held and many researchers in the field of the digestive tract in particular greatly welcomed the opening of the Biwako Symposium.

I should like to take this opportunity to express many thanks to Dr. Shiro Hosada, symposium chairman, Dr. Tadao Bamba, Professor of Shiga University of Medical Science as general secretary of the symposium, many other doctors of its second internal department, and Eizai Co. Ltd., as the symposium sponsor, especially Mr. Nobukatsu Hashimoto, managing director of Eizai for their kind and continuous cooperation for bringing the symposium into successful existence for the past 5 years.

I am also pleased that the Japanese version of the collection of research reports of the symposium has already been issued every year and that this year this collection will also be published in English in a special of ‘Digestion’, an authoritative medical journal.

In addition, I would like to highly evaluate that at this Biwako symposium the followers of the late Masasuke Masuda, professor emeritus of Kyoto Prefectural University of Medicine who enthusiastically expected rapid development in small intestine disease research in Japan, Prof. Shiro Hosoda and Prof. Tadao Bamba very energetically contributed to spurring on the development of research.

The symposium was originally planned to be held for 3 years, but has taken place five times with great achievements towards our goals.

As a representative of the advisors of the symposium, I hope the Biwako International Symposium will be held again in a not too distant future.

Tadayoshi Takemoto
President Emeritus,
Japanese Society of Gastroenterology
Professor Emeritus,
Yamaguchi University School of Medicine
Looking Back Upon the Biwako Symposium

The first Biwako Symposium was held in 1995 and the fifth and final one in 1999. As suggested by its formal name, the Eisai Biwako Symposium ‘Intestinal Mucosal Damage and Repair’, this was an event sponsored by Eisai Co. Ltd. to promote new developments in a very narrow field of the subspecialty of gastroenterology and hepatology. Through Eisai’s sponsorship, specialists gathered once a year for two days and one night in Otsu City, on the scenic shores of Lake Biwa, to thoroughly discuss basic and clinical research in this least-explored field of gastroenterology and hepatology.

These symposia were organized by Program Committee members, who were distinguished representatives of Japan’s specialists in this field. They selected the subthemes and presenters for each symposium working under the leadership of the Executive Director, Tadao Bamba, Professor of the 2nd Department of Internal Medicine, Shiga University of Medical Science. Tadayoshi Takemoto, who is Professor Emeritus and former Director of the Japanese Society of Gastroenterology, served as Special Advisor. I would like to express my profound gratitude for his guidance in everything from conceptualizing to planning the first of these Symposia and for his participation in each of them.

The proceedings of all five symposia were prepared in Japanese. However, following the fifth symposium, it was decided to publish a portion of the proceedings of all five of the Symposia in English. And, with the cooperation of S. Karger AG, this work has been completed.

As Chairman of the effort to produce this publication, I am honored to have been given the opportunity to write its preface. I dedicated my entire career, from the time I graduated from the Kyoto Prefectural University of Medicine in 1952 and joined the 3rd Department of Internal Medicine to my retirement from the 2nd Department of Internal Medicine, Shiga University of Medical Science in 1994, to research in this field.

It pleases me that the Biwako Symposia have helped to further developments in the fields of pathophysiology, pathobiochemistry and immunology research of gastrointestinal mucosa, and that the symposia have contributed to the treatment of patients with intractable inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis. I will close by saying that I am confident that, in the near future, we will fully understand the etiology of these diseases and will be able to treat the patients.

Shiro Hosoda
Chairman, Biwako Symposium
Professor Emeritus,
Shiga University of Medical Science