

# ENDOTOXIN NEWSLETTER



## HISTORY AND ACTIVITY OF THE JAPANESE ENDOTOXIN SOCIETY

Masayasu Nakano,  
Jichi Medical School

Approximately 170 endotoxin researchers from all over Japan gathered at the General Culture Center in Utsunomiya, located 100 km north of Tokyo, on November 23 and 24 to attend the 6th Annual Meeting of the Japanese Endotoxin Society. The meeting consisted of 37 presentations, including 4 special lectures. In one of the lectures, S. Akira presented his excellent new data on signaling pathways through Toll-like receptors (TLRs) stimulated not only with LPS but also with other bacterial components. TLRs were the focus of much attention and were the subject of a symposium, and K. Miyake and other speakers discussed the topic enthusiastically. The structure-function relationships of low-toxicity endotoxins from oral bacteria and *Helicobacter pylori* was the topic of another symposium, and presentations on this topic were given by T. Ogawa, K. Amano, K. Tanamoto and others. Strategies for prevention and therapy of septic shock were also main topics of discussion for clinicians, and one symposium was conducted for them. K. Imaizumi reported on the effectiveness of blood dialysis using polymyxin B-fixed fiber column in shock patients with Gram-positive as well as Gram-negative bacterial infections, and several other promising procedures and chemicals for prevention of shock were discussed by others in the symposium.

The first endotoxin research in Japan was conducted at Tokyo University in the 1930s. During the period of World War II, it became very difficult to continue research in universities and, at the terminal stage of the War, all centers of scientific research in Japan were destroyed completely. Research in the biological sciences, including endotoxin-related research, was resuscitated in the 1950s. In 1955, the first domestic meeting on biological toxins was held, in which not only bacterial toxins were considered but also toxins from other organisms such as fungus, insect, fish, and snake, and researchers active in the endotoxin field participated in the meeting. This meeting has occurred annually ever since and has continued to attract presentations by many basic endotoxin researchers. On the other hand, clinical doctors engaged in endotoxin research gathered and established the Clinical Endotoxin Society in 1987, and their meeting was held once every two years. In the 1990s, a couple of other endotoxin research groups also sprung up in Japan, and these groups held meetings without connection to other endotoxin groups. There was neither intimate contact nor information exchange among these groups.

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#### Newsletter Editor

Kent R. Myers, PhD  
Corixa Corporation  
553 Old Corvallis Road  
Hamilton, MT 59840-3131 USA  
Tel: 001-406-375-2135  
Fax: 001-406-363-6129  
E-mail: kmyers@corixa.com

#### Website Editor

Carl R. Alving, MD  
Chief, Dept. of Membrane Biochemistry  
Walter Reed Army Institute of Research  
503 Robert Grant Road, Room 2A24  
Silver Spring, MD 20910-7500 USA  
Tel: 001-301-319-9611  
Fax: 001-301-319-9035  
E-mail: carl.alving@na.amedd.army.mil

### Input Needed For IES Website Links

A proposal to include links to the homepages of members as well as to companies that make endotoxin-related products is currently being considered in the IES website ([www.kumc.edu/IES/ieshome.htm](http://www.kumc.edu/IES/ieshome.htm)). It is thought that this will increase the usefulness of the website for researchers in the endotoxin field. Participation by members would of course be completely voluntary. The companies would be those that provide products or services related to endotoxin (e.g., high purity endotoxins, reagents for removal of endotoxin from proteins, anti-endotoxin antibodies, etc.). The company listings would include a brief description of the products offered and a link to the company's website, and would be provided at no charge to the company.

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Comments from the membership on this proposal are being sought. We are especially interested in receiving suggestions for companies that should be listed on the website. Please include the name and email address of the contact person at each recommended company. Comments and suggestions may be sent to Robert Munford at [robert.munford@utsouthwestern.edu](mailto:robert.munford@utsouthwestern.edu). □

**Editor's note:** Arthur Johnson and Johanna Schlosshardt were named as recipients of the Honorary Life Membership awards for 2000 and 2001, respectively, at the recently held Paris 2000 conference (see the IES Newsletter, vol. 10, no. 3). The following two articles provide an introduction to Dr. Johnson and his distinguished career. In the first article, Dr. Johnson deftly sketches his life as an immunologist and an endotoxin researcher, and he provides a fascinating perspective on some of his major contributions. This article was written at the request of Ernst Riestchel, a lifelong colleague and friend of Dr. Johnson's and the person who announced the award at the Paris 2000 meeting, and in the accompanying article Dr. Riestchel provides his own view of Dr. Johnson and his career. The life and career of Dr. Schlosshardt will be the subject of a future article in the Newsletter.

# MY SCIENTIFIC AUTOBIOGRAPHY

Arthur G. Johnson, Professor Emeritus,  
University of Minnesota

My professional studies began in 1946, after serving three years in the U.S. Merchant Marine. I graduated from the University of Minnesota in 1950, majoring in Physiological Chemistry with a minor in Microbiology. The latter included a course in Immunology from Dennis Watson, in which I got hooked on his vision and infectious enthusiasm, and became a graduate student in his laboratory. The problem we studied involved the effect of massive antigen dosage on the development of immunologic lesions. However, when our sole source of financial support was found to be with child (Louise was a statistician at Minneapolis Honeywell), we took advantage of a request in 1952 by Maurice Landy of the Walter Reed Army Institute of Research in Washington, D.C., to fill a junior immunologist position. The problem under study was the improvement of typhoid vaccine by isolating and purifying the two major antigens, Vi and O, such that effective immunogenicity might be retained with elimination of the well-known toxicity of the whole organism. The Vi antigen turned out to be an aminogalactouronic acid which was highly protective in animal tests without any toxicity. In purifying the O antigen, we started with the Boivin product, and with the expertise of our two biochemists, Marion Webster and Jerry Sagin, and through ammonium sulfate precipitations in the presence of high concentrations of sodium chloride, we ended up with a lipopolysaccharide with only 0.6% nitrogen, of which 0.4% was attributable to hexosamine. Such preparations were antigenic but were much less protective than the Vi antigen. They also exhibited potent endotoxic activity.

As part of the spin off of that effort

resulting in the availability of a purified endotoxin, we tested the lipopolysaccharide for any contribution it might make to the previously observed adjuvant action of mixed vaccines which employed Gram-negative bacteria as one of their constituents. Inclusion of *Hemophilus pertussis* vaccine with diphtheria and tetanus toxoids had been found by others to result in higher antitoxin titers than when each toxoid was injected singularly. Accordingly, we tested the response of rabbits to ovalbumin (a purified protein antigen which could be measured with analytical precision), with and without a few micrograms of our purified LPS. Lo and behold, the anti-ovalbumin antibody response of the rabbits receiving the LPS was extraordinarily high! Similar responses were achieved with diphtheria toxoid and numerous other antigens. These results formed the basis of my Ph.D. thesis conferred by the University of Maryland in 1955.

We moved to the University of Michigan in the fall of 1955 and initiated a program of study of factors affecting the adjuvant action of the endotoxin. The time of administration of LPS relative to the antigen proved to be important. Thus, injection of endotoxin close to the time of administration of antigen resulted in the adjuvant response, while LPS injection 1-2 days before antigen, surprisingly, resulted in suppression of the immune response. In addition, host immunocompetent cell division was increased by LPS and found to be basic to the adjuvant action.

Working with pathologists Peter Ward and Murray Abell, we studied histological reactions in rabbit tissues during the adjuvant action of LPS. Observations which influenced us the most were the increased response of germinal centers and the disrupted appearance of lymphocytes following

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## Arthur G. Johnson

Ernst Th. Riestchel, Prof. Dr.,  
Forschungsinstitut Borstel

In 1968, I joined the laboratory of Otto Lüderitz at the Max-Planck Institute for Immunobiology in Freiburg, which is located in the beautiful scenery of the Black Forest. The first scientific seminar I attended in the Institute's library was given by a certain Arthur G. Johnson, apparently a friend of Otto Lüderitz, Otto Westphal, and Herbert Fischer. Art talked about the adjuvant action of lipopolysaccharides and – unforgettable for me – developed the idea that endogenous nucleic acids liberated by immune cells may be mediating this impressive property of endotoxins. This first seminar was a disaster for my scientific ego: Having been trained as a pure synthetic chemist and not knowing anything about antibodies, lymphocytes, and the immune system, I could not follow Art's argumentations. After the seminar, Otto's group (which included at that time Mireille Berst, Günther Hämmerling, Peter Mühlradt, Wulf Dröge, Dieter Malchow, Chris Galanos, and others) went for dinner with Art in a restaurant at the Kaiserstuhl, where fresh asparagus and Ihringen wine was served. During this evening, Art explained to me with great patience and kindness his scientific findings and ideas in very simple terms. I was very honoured and excited. In retrospect it is fair to state that this encounter was an important impact for me to engage myself in the study immunology.

I met Art again in 1971, when I was a postdoc at the University of Minnesota, Minneapolis, in the laboratory of Dennis W. Watson, the scientist who had first taught immunology to Art. Since then, our ways have crossed many times on the occasion of international meetings in

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Europe, Japan, and the USA, some of which had been organized by Art himself!

Arthur Gilbert Johnson was born on February 1, 1926, in Eveleth, Minnesota. He is married, since 1951, to Louise, and the Johnsons have three children. During his professional life, Art was a visiting Professor at the Stockholm University, Stockholm, Sweden, and the Institut Pasteur, Paris, France. He served on many NIH and governmental site visit committees, was Editor of *Infection and Immunity* (1977-1986) and trained over 50 students and postdoctoral scholars, now occupying important positions. These include Professors Phyllis Kind, Yi-Chi Kong, Katherine Merritt, Jon A. Rudbach, Alice Jacobs, Jon Schmidtke, Alex Abdelnoor, Robert Cone, Sandra White, Booe Ma, Howard Lederman, and others.

I had asked Art to help me in writing his scientific *curriculum vitae* in a more personal way. He wrote a few pages and after reading them I felt that they should be published as they stand, without additions, changes or any editorial commenting. The pages Art wrote do best illustrate his personality and character – combining scientific excellence with modesty and friendliness. Art is a pioneer in the immunology section of endotoxin research, a wonderful person, truly meriting the honour of having been elected as Honourary Life Member of the IES. □

## Autobiography

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endotoxin *in vivo*. Since the lymphocyte has a very high nuclear to cytoplasmic ratio, we formulated the hypothesis that LPS released nucleic acid fragments which stimulated the immunocompetent cells to function more rapidly and to a greater degree. Support for this hypothesis was gained with our demonstration that homologous and heterologous nucleic acids, as well as nuclease derived oligonucleotides, also non-specifically stimulated antibody formation. Later when Braun and Nakano found synthetic polynucleotide complexes also functioned as adjuvants, we characterized their action on T cells and macrophages in detail. We concluded, however, that those endogenous products did not mediate the adjuvant action of LPS.

Other studies included demonstration of the effect of human serum in neutralizing several properties of the endotoxin, assessment of the properties of endotoxoids with Andre Nowotny, and those of monophosphoryl lipid A with the Ribi group, as well as the synthetic analogs of the Hasegawa group. We also characterized the ability of LPS to elevate the antibody response of aging mice. In addition, the capacity of LPS and polynucleotide complexes to increase substantially non-specific protection against cytomegalovirus was observed.

In 1978, we moved to the University of

Minnesota, Duluth, assuming the chair of Microbiology and Immunology. We continued with our pursuit of the mechanism of action of both the endotoxin and poly A:poly U complexes as adjuvants and as non-specific stimulants of host resistance to viruses. The results of many studies established the sites of action of these adjuvants on T cells and the macrophage, albeit by different mechanisms. Cytokine release appeared to mediate the adjuvant and suppressive action of both, with interferon gamma, tumor necrosis factor alpha and transforming growth factor beta responsible in the main.

My teaching involved both Immunobiology and Advanced Immunobiology graduate courses, in addition to those on Microbiology and Immunology to freshman and sophomore medical students, both at the University of Michigan and University of Minnesota, Duluth. I retired to Emeritus status on February 1, 1999, and am continuing to lecture occasionally and do some writing.

I feel truly honored to receive honorary life membership in the International Endotoxin Society, and wish to thank my many colleagues and students who have been a constant source of intellectual stimulation over these many years! What a challenging experience it has been to try to understand more fully the many diverse properties of this fascinating molecule! □

## History and Activity of the Japanese Endotoxin Society

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In May, 1988, the International Endotoxin Symposium was held at Jichi Medical School near Utsunomiya under the sponsorship of the Jichi Medical School and the newly formed International Endotoxin Society (IES). The IES adopted the constitution at the general meeting in the Symposium and decided to hold the first IES Conference in San Diego in 1990. Encouraged by the establishment of the IES, the many Japanese endotoxin researchers decided to unify into a single society. The Japanese Endotoxin Society (JES) was established in the fall of 1994 through the dedicated efforts of N. Kato, M. Kodama, S. Tamakuma, T. Yokochi, M. Yoshida and others. It was decided that the society would meet every year at a different location and the first meeting of the JES was held in the fall of 1995 in Yokohama under the direction of G. Shimada. The next meeting was held in association with 4th Conference of IES in Nagoya in October 1996 and was chaired by T. Yokochi. The third through fifth meetings were held in Kyoto in 1997 (chaired by M. Kondo), in Tokyo in 1998 (chaired by M. Onda), and in Beppu, Oita in 1999 (chaired by S. Yamamoto).

JES now has 306 registered members. Included among the membership are 197 clinical doctors, including 111 surgeons, 38 physicians, 17 emergency doctors, 11 anesthesiologists, and 8

internists. Fifty-five of the non-clinical investigators are associated with medical, dental or pharmacological institutions, and the rest of the members are basic scientists. One third (34%) of IES members are working in Tokyo metropolitan-Kanto area, and 25% are in Kansai area (Osaka, Kyoto, Nara, Kobe, etc.). The Kyushu area (second larger island located in south of Japan; includes Fukuoka, Kurume, Oita, Saga, etc.) accounts for 14% of the membership, and the Nagoya-Chubu area, located in between Kanto and Kansai, has 10%. The Tohoku area (north part of main island; includes Morioka, Akita, etc.) contains 6% of the membership, Chugoku-Sikoku area (south part of main island and its adjacent 4th bigger island) has 8%, and Hokkaido area (third bigger island located in north of Japan; includes Sapporo) has 3% of the researchers.

The IES Conference in the year 2004 is once again going to be held in Japan. The JES is delighted very much with this decision, and we will help the 2004 Conference to be successful to the best of our ability. The JES can be contacted at: Japanese Endotoxin Society, c/o Department of Surgery, Shiga University School of Medicine, Otsu, Japan 520-0021, Phone: 81-77-548-2238, FAX: 81-77-548-2240. □

## Change of Address

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It is important that the IES maintain an accurate list of current members. Please send all notices of change of address to Dr. Richard Silverstein at:

Richard Silverstein, PhD, IES Secretary  
Dept. of Biochemistry  
Kansas University Medical Center  
3901 Rainbow Blvd.  
Kansas City, KS 66160-7421 USA  
Phone: 001 913 588 6954  
Fax: 001 913 588 7440  
E-mail: [rsilvers@kumc.edu](mailto:rsilvers@kumc.edu)



## Email Directory in Progress

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The IES is striving to create an email directory. A message was recently sent to all members with known email addresses. If you did not receive a message, please take this opportunity to provide an updated address, phone, fax, and/or email address for your listing by sending a brief email immediately to [njpollman@hotmail.com](mailto:njpollman@hotmail.com).

## Submissions Requested

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Do you have any news, questions, or comments that you think may be of interest to your colleagues in the IES? If so, the Newsletter would love to hear from you! We welcome submissions of just about any sort, including news items, meeting announcements or summaries, announcements of available positions, historical matters, photographs, and other pertinent (or otherwise) drolleries of potential interest to the membership. While the Newsletter does not expect to serve as a technical journal for publication of original research results (that is the function of the *JER*), it is an appropriate forum for discussion of any and all issues related to the endotoxin community. Please submit all items for publication in the Newsletter to the Editor at the address shown on p. 1.

## Missing Newsletter Issues?

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If you are an IES member and believe that you may have missed an issue of the IES Newsletter, please notify the Newsletter Editor at the address shown on p. 1.

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International Endotoxin Society  
c/o Kent R. Myers, PhD  
Corixa Corporation  
553 Old Corvallis Road  
Hamilton, MT 59840-3131  
USA