



PARIS 2000 MEETING TO HIGHLIGHT TLRs, SEPSIS

The emerging understanding of the molecular events involved in LPS recognition and signaling will be a major theme at the upcoming IES conference, to be held at the Pasteur Institute in Paris on August 24-27. As shown below, the oral program will feature several presentations on Toll-like receptors (TLRs) and their role in LPS signaling, and will continue to develop the paradigm that LPS (endotoxin) recognition is one facet of a general system of innate immunity that is directed against microbial challenge. Additional presentations will describe recent research on the downstream events triggered by LPS, new strategies to disrupt these events clinically in the prevention and treatment of sepsis, and the regulation of lipid A biosynthesis. The conference also includes a program of poster presentations that, judging from the programs at previous IES conferences, will provide vigorous and comprehensive coverage of all areas of endotoxin research. Anyone engaged in endotoxin-related research should make plans to attend this meeting – it's not too late to register! Further details on the program and on all other aspects of the conference can be found at the conference website (www.pasteur.fr/recherche/unites/ies2000).

Keynote speaker

Charles Janeway (Yale School of Medicine, New Haven, CT) - *The Toll Family of Proteins and Their Ability to Signal the Presence of Endotoxin Bound to CD14*

Toll-like Receptor Mediated Signalling

Bruce Beutler (University of Texas, Dallas, TX) - *Functions of Toll-Like Receptors*

Sankar Ghosh (Yale University, New Haven, CT) - *Signaling through Tolls*

P. Godowski (Genentech, San Francisco, CA) - *TLR-Mediated Signaling*

Douglas Golenbock (Maxwell Finland Lab, Boston MA) - *Roles for TLR2*

J. Han (TSRI) - *LPS-Initiated Signaling*

Shun Kawabata (Japan) - *Limulus TLRs*

R. Medzhitov (Yale University, New Haven, CT)

K. Miyake (Saga Medical School, Japan) - *Innate Recognition of Lipopolysaccharide by the Members of the Toll Family TLR-4-MD-2 and RP105-MD-1*

Shizuo Akira (Hyogo College of Medicine, Japan) - *Phenotypes of TLR Knockout Mice*

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Volume 10, Number 2
Spring 2000

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INSIDE:

A Word From Our Treasurer

Dr. Kuni Takayama,
IES Treasurer

The International Endotoxin Society (IES) is solely responsible for organizing and financing the biennial IES Conference in Paris on August 24-27, 2000. This is the meeting where all of the important studies conducted internationally within the last two years on endotoxin/lipopolysaccharide are reported at a single site. We would like for this meeting to be self-supporting. In order for this to occur, we need the support from two major sources of income: corporate contributions and revenue from paid attendance at

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The IES Needs You!

Dr. Tony Rudbach, IES Secretary

Inasmuch as my final term as IES Secretary expires this summer, you will be spared hearing my message again. But I need to make my plea one more time before I am in a terminal state.

A "volunteer" is a person who offers to enter into a service of his/her own free will, usually without thought of compensation. The IES, your society, is run exclusively by volunteers. Shortly, the incoming IES President, Dr. Robert Munford, will be seeking to fill positions on many of the committees that "run" the IES. These include committees on Nominations, Membership, Investment, Local Meeting Host, Fundraising, Publications, and Elections. Many times it is from the ranks of these volunteer committees that candidates for IES officers, Councillors, and the Scientific Program Committee are picked.

I would especially encourage the younger and mid-career IES members to think about service to the IES. In addition to benefiting the Society it will enhance your resume and give you something to fill in portions of forms asking for participation in National/International organizations. There is no stigma attached to volunteering; just send a note or an e-mail to me or to the new IES Secretary, indicating your willingness to serve and in what capacity. We will see that the information gets to President Munford.

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Paris 2000 Program

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CD14

Theo Kirkland (University of California, San Diego, CA) -
Structure-Function Studies of CD14

LPS-Initiated Pulmonary Injury

Tom Martin (University of Washington, Seattle, WA) -
LPS, ARDS, and Apoptosis

Jérôme Pugin (University of Geneva, Switzerland) -
Recognition of Bacteria and Bacterial Products in the Lung

David Schwartz (University of Iowa, Iowa City, IA) - *TLR4 Mutations Cause Endotoxin Hyporesponsiveness in Humans*

LPS-Initiated Hepatic Injury

Tim Billiar (University of Pittsburgh)

Lyle Moldawer (Florida College of Medicine,
Gainesville, FL) - *Endotoxin-Induced Hepatic Apoptosis*

LPS in the Clinic

Tim Axtelle (ICOS Corporation, Bothell, WA) -
Clinical Trials with Anti-CD14

Charles Fisher (Eli Lilly & Co., Indianapolis, IN) -
Clinical Trials in Sepsis

Robert Munford (University Texas Medical Center, Dallas, TX) - *Heretical Thoughts on Therapy for Sepsis and SIRS*

Kevin Tracey (North Shore Community Hospital)

Jean-Louis Vincent (Erasmus Hospital, Brussels, Belgium) -
Sepsis

LPS Biochemistry and Biosynthesis

R. Kitchens (University Texas Medical Center, Dallas, TX)
- *LPS-Cell Membrane Interactions*

Chris Raetz (Duke University Medical, Durham, NC) -

Regulation Lipid A Biosynthesis in E. coli and Salmonella
Samuel D. Wright (Merck Research Labs, Rahway, NJ)

LPS and Clotting

Tom van der Poll (University of Amsterdam, Netherlands)

Treasurer's Report

(Continued from previous page)

the meeting. Thanks to an outstanding fundraising effort made by many IES members, we have exceeded our goal for corporate contributions. The financial success of this meeting now rests on the final attendance figure. The latest figures suggest that we are getting close to this goal. On behalf of the IES Officers, I urge all members to show your support for the IES by attending this intellectually stimulating meeting at the most fascinating and culturally rich city in the world. With a

good membership turnout, we can ensure a financially successful meeting.

To those of you who have yet to pay your 2000 IES membership dues, we urge you to do so now. We have a convenient (now a very popular) method of payment by credit card. Credit card payments can be Faxed directly to Linda Amrhein at (608) 262-8418. I will also accept dues payment by mail/E-mail/Fax. You will have to provide the credit card number, name of the card (VISA or MasterCard only), its expiration date, your name as it appears on the card, the amount of payment (US \$45.00), and your signature.

Other details are on the IES website at <http://www.kumc.edu/IES/duesinfo.htm>.

If you plan to attend the Paris 2000 IES Conference, you should send in your IES membership dues since a member in good standing gets a 20% discount on the meeting registration fee.

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JER Update

Jack Levin, M.D., JER Editor-in-Chief

This issue of the IES Newsletter contains the Table of Contents of the *Journal of Endotoxin Research* for the final issue of Volume 5 for 1999. As you can see, this list of original research papers provides an example of the wide range of scientific areas that are now represented in the pages of the JER. It is also noteworthy that these contributions are from biomedical research laboratories around the world, thus reflecting the international membership of the IES (see the article by Dr. Silerstein on p. 6).

We have successfully completed the first year of publication of the reborn journal, now published by Maney Publishing. I continue to invite you to not only subscribe to the official journal of your society but, equally important, to submit a manuscript for publication. I can promise an efficient review process and rapid publication of accepted contributions. Subscriptions, available at

a personal membership rate of US \$78, are also encouraged. Information on the Journal can be found on the enclosed subscription form, at www.kumc.edu/IES/jerc.htm, or by contacting me at the address shown below:

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Table of Contents for *Journal of Endotoxin Research* Volume 5, Numbers 5/6, 1999

Research Articles

LPS pretreatment of mouse peritoneal macrophages differentially modulates TNF α and iNOS expression

N. Hirohashi, M.-G. Lei, D. C. Morrison

Analysis of structure activity relationships for LPS-mimetic activities of taxane analogs in murine macrophages

P.-Y. Perera, J.F. Kadow, C. R. Fairchild, K. A. Johnston, S. N. Vogel

Potential role of bacterial lipopolysaccharides in the development of autoimmune gastritis induced by neonatal thymectomy

H. Kodaira, T. Mizoroki, H. Shimada, K. Ishii, M. Hosono, Y. Kumazawa

Effect of ebrotidine on *Helicobacter pylori* lipopolysaccharide-induced up-regulation of endothelin-1 in gastric mucosa

B. L. Slomiany, J. Piotrowski, A. Slomiany

Polysaccharide and lipid components of *Bacteriodes thetaiotaomicron* lipopolysaccharide as stimulators of endothelial adhesion molecule expression

A. Rokosz, F. Meisel-Mikolajczyk, C. Malchar, M. Nowaczyk, A. Górski

LPS sensitivity in recombinant mice lacking functional alleles at MHCII, *Lps* and *Nrampl* genes

A. D. Wright, S. K. Chapes

Signal transduction pathways involved in lipopolysaccharide-induced production of PGE₂ by human microvascular endothelial cells

K. A. Lucas, J. T. Flynn

Dissociation of IFN- α from IL-12 and IL-18 production during endotoxin tolerance

N. Rayhane, C. Fitting, J. M. Cavillon

This is the conclusion to a two part article based on a fascinating presentation given by Professor Rietschel on September 14, 1998, at the 5th IES Conference which was held in Santa Fe, New Mexico.

Immortal Music and Deadly Septicemia: Death of famous composers by bacterial blood poisoning

Ernst Th. Rietschel
Research Center Borstel
Center of Medicine and Bio-Sciences
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Parkallee 22, D-23845 Borstel

Alban Berg

When Scriabin dies in 1915, a composer in Vienna is working on an opera, which he calls "Wozzeck". It represents a key piece of work for the new music, and is based on the drama fragment "Woyzeck" of Georg Büchner telling the story of a haunted person - the great composer I am talking of is **Alban Berg**.

Room is missing to talk in detail about the life and the wonderful new music of this composer. It will have to be enough to state that Berg gained world-wide fame by his dodecaphonic operas *Wozzeck* and *Lulu* and revolutionized the art of composing by introducing short motifs which determined a whole piece of art. He spent all his life as a productive artist together with his wife Helene in a Vienna suburb, in Hitzing.

In the year 1935, however, in the days of completion of the violin concerto, Berg gets an insect sting on the lower part of the spine that becomes seriously inflamed. An abscess develops turning over to furunculosis and despite surgery Berg suffers from severe sepsis. His medical supply is inadequate and a blood transfusion, carried through at home, only results in temporary ease. The deadly blood poisoning inexorably takes its course and on December 24th, 1935, Alban Berg dies of septic multi-organ failure at the age of 50.

Gustav Mahler

Among Alban Berg's role models we find the idol of the whole musical youth in Vienna of that time: **Gustav Mahler**. Gustav Mahler was born on July 7th, 1860 as one of 12 children, three of whom only reached the age of 16 years. Thus, death

was with Mahler from youth on. Still being young he becomes famous as a conductor and in 1897 finally, he was nominated chief conductor of the Royal Opera in Vienna - a dream position. A meteoric advancement as a conductor, in the beginning less as a composer, was granted to Mahler, and he fast became an international celebrity. In 1901, when Mahler, at the age of 41, is always the centre of attention in Viennese social life, he meets the beautiful and flourishing Alma, being his junior by 20 years, the daughter of the landscape painter Emil Jakob Schindler. He marries her on March 9th, 1902 in Vienna.

Dr. Emanuel Lipman, of Mount Sinai Hospital, examines Gustav Mahler and is the first to make the right diagnosis of *Endocarditis lenta*, or inflammation of the heart valves by streptococci. Lipman informs Mahler of this diagnosis and hopeless prognosis.

Right from the start the marriage was overshadowed by Mahler's instable state of health. The holiday months are problematic as well. Mahler uses them to compose from dawn to dusk. In 1905 he composes the "Songs on the Death of Children" (*Kindertotenlieder*), without knowing that

two years later his beloved elder daughter Maria Anna was to die of diphtheria. Alma Mahler regarded the musical arrangement of the "Kindertotenlieder" as a temptation of fate. After the terrible death of the 5-year-old daughter Maria Anna in 1907, mother Alma complains of heartache and a doctor is called who, however, cannot find anything particular and only prescribes rest. More driven by coquetry than by acute complaints, Mahler asks the physician to examine him as well. The doctor diagnoses a clear heart condition. This diagnosis came as a bombshell to Mahler, news of which he actually should never recover.

In 1907 as well, Mahler retires from his high position in Vienna after nerve-racking disputes and intrigues and accepts an engagement as chief conductor of the Metropolitan Opera in New York. There he composes drafts of a 10th symphony. On February 20th, 1911 in New York, a fever attack occurs with a sore and coated throat accompanied by a circulatory collapse. Mahler's family practitioner, Dr. Fraenkel, contacts the New York doctor Emanuel Lipman of the Mount Sinai Hospital, who is the first to make the right diagnosis of *Endocarditis lenta*, i. e. inflammation of the heart valves by streptococci. Lipman informs Mahler of this diagnosis and hopeless prognosis.

Last hope is expected from one of the famous bacteriologists in Paris such as the Nobel Prize winner **Ilja Metchnikov**. Therefore the family returns to Europe by ship in April 1911. They go to Paris to see Metchnikov but do not reach the famous scientist due to the Easter holidays. Instead they consult a well-known parisian infectious diseases doctor, Dr. **André**

Chantemesse. Chantemesse takes a blood sample, and Alma Mahler writes about the circumstances of this examination in her memoirs, "Chantemesse, the famous bacteriologist, now made a pure culture with Mahler's blood - oh, doctors! After a few days he appeared - beaming - with a microscope. Should a wonder have happened? He adjusted the microscope on the table, 'Look, Mme. Mahler, I myself have never seen streptococci developed so fabulously. Look at these strings - they are algae.' He wanted to explain, to shine! But I could not hear anything. Almost faint with pain I left him."

Mahler wants to die in Vienna, to where he is brought with the Orient Express. He is suffering and tormented, finally receives morphine, and in the evening of May 18th, 1911, he succumbed to a severe bacterial sepsis at the age of 51 after a long death agony. He dies during a thunderstorm like Beethoven 84 years earlier.

In 1913 Arnold Schönberg makes a commemorative speech on Gustav Mahler in Prague in the course of which he also talks about the last works of Mahler. So he says about Mahler's 10th symphony, "What his Tenth was meant to say to us, we will know as little about it as in the case of Beethoven and Bruckner. It seems as if the Ninth is the limit. The one who wants to go beyond has to leave. It looks like the Tenth could tell us something that we shall not yet know, for what we are not yet mature. Those who wrote a Ninth were too closely connected to the other world. Maybe the mysteries of this world would be solved if somebody who knows about them wrote the Tenth. And that is probably not intended to be."

Ottorino Respighi / Conclusion

Let us glance backwards and at the same time forwards: During the time of Louis XIV until the end of the 19th century, doctors and scientists had no idea of the aetiopathogenesis of an infection, not to mention of how a septic disease is caused or even can be healed. Of course, clinical science and medical microbiological research still had to develop. In the 19th century, they had advanced far but were not enough popularized and supported. Today, research is undoubtedly better promoted, but for certain not yet to a sufficient degree.

This could have fatal consequences, as we have to learn in these years, since infectious diseases are about to return and sepsis remains to represent one of the most common causes of death of patients in intensive care. That is why we need more than ever a most intensive and widely diversified research activities in the field of infections. Due to the development of resistances, rapid spread of infectious agents, tourism, dramatic urbanization, the appearance of so far unknown infectious agents, infectious diseases will for certain gain increasing importance. Then it is for us doctors and scientists to lay our cards on the table. Such a kind of helplessness of doctors and scientists towards infectious diseases as at the time of Louis XIV must never occur again. Therefore, at this point the appeal is made to politics and society: "Do promote basic research and patient-oriented research of infections. Together with Rodney Nichols, president of the New York Academy of Sciences, I would like to proclaim: If you think the study of infectious diseases and education are expensive, try ignorance and disease."

Ottorino Respighi's wife Elsa has to lie to her husband, following the advice of the family doctor: she tells him that he is only suffering from a harmless *E. coli* infection with no threatening consequences.

It is interesting to realize that parallel to the development of antibiotics and the preliminary end of infectious diseases, classical music reached an almost inaccessible, artificial impasse where it could no longer be judged whether a composer was

an artist or a charlatan. The one who already in the thirties realized that music was developing to a dead end was **Ottorino Respighi**, born in 1879 in Bologna. The basic character of Respighi's creative work consists in an attempt to create a balance between tradition and progress, similar to Alban Berg but nearly always in a tonal and completely other way. His masterly talent for orchestration and the brilliant colouring of his arrangements are most impressively shown to advantage in his transposition of Bach's chorale "Wachet auf, ruft uns die Stimme" (Sleepers wake! loud sounds the warning"). With this chorale I also want to end my lecture in a few minutes.

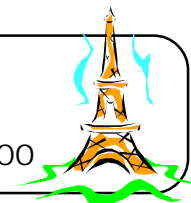
In the last months of the year 1935, Respighi's thoughts revolve around his last work, an opera entitled "Lucrece" (according to Shakespeare's "The rape of Lucrece"). He works feverishly, struggling against a chronic, unexplicable fatigue. This is probably connected to a slowly increasing bacterial infection which haunts and weakens him more and more towards the end of the year 1935.

In January 1936 finally, *Endocarditis lenta* is diagnosed and *Streptococcus viridans* bacteria are isolated from Respighi's blood. Ottorino Respighi's wife Elsa has to lie to her husband, following the advice of the family doctor: she tells him that he is only suffering from a harmless *E. coli* infection with no threatening consequences. In March, Respighi writes the last notes of his opera "Lucrece". But the hour of his death is inexorably approaching. During his last days, Respighi is still procured with sulfonamides from Berlin, since Gerhard Domagk just published the discovery of "Prontosil". But the therapy takes no effect, probably above all because the sepsis has already progressed too far.

On April 18th, 1936 at 6 o'clock in the morning, Respighi dies of septic shock and with him one of the masters of music. The minutes of his death agony are accompanied by rain and storm, thunder and lightning, like in the case of Beethoven and Mahler, but when Respighi closes his eyes forever a nightingale is singing.

Please visit our IES PARIS 2000 website to view a link to the Paris Tourist Information Office.

www.pasteur.fr/recherche/unites/ies2000



We Are At 48...

Dr. Richard Silverstein, IES Membership Secretary

No, it is not the age of our Society... at least not yet! It is the number of countries, spanning 6 continents (we have not heard from Antarctica yet), from which the IES continues to draw its more than 600 members. That's up from 41 countries in 1994. Specifically, the IES has members from:

Australia, Austria, Belgium, Bolivia, Bulgaria, Canada, Chile, China, Colombia, Cuba, Czech Republic, Denmark, England, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Iran, Ireland, Israel, Italy, Japan, Lebanon, The Netherlands, Nigeria, Northern Ireland, Norway, Poland, Romania, Russia, Saudi Arabia, Scotland, Singapore, Slovak Republic, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Ukraine, United States, Wales.

..... and growing

There has been a marked increase in the rate at which new members continue to join. Between 1995 and 1998, the annual increases in new members were 25, 15, 9, and 25 per year. In 1999, this increased to 64 new members for the year. As we continue through the year 2000, there were, even as of May 2nd, yet an additional 62 new members, representing a wide range of scientific interests in endotoxin.... still another demonstration of our *raison d'être*. Tell a colleague about the IES today. Information on becoming a member can be found at www.kumc.edu/IES/htm.

Nominations Still Open For Honorary Lifetime Members

Dr. Tony Rudbach, IES Secretary

You may still nominate a deserving individual for Honorary Lifetime Membership in the IES. Each year, one endotoxin researcher may be designated as an Honorary Life Member of the Society as a tribute to his or her contributions to the knowledge and understanding of bacterial endotoxins. Two individuals to be considered for this honor shall be identified biennially; one each year between the biennial IES Conferences. Election to Honorary Life Member will be by a two-thirds majority vote of the membership in attendance at the biennial business meeting. Honorary Life Members have all the rights and privileges of active members but are exempt from Society dues

and meeting registration fees. Please send nominations, in the form of a letter describing the nominees history of achievements in endotoxin research, to:

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Welcome

Also, welcome back to
all past members that
have re-joined!

Change of Address

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

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Hello, Anybody There?

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?

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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