ESS Spring Newsletter 2016

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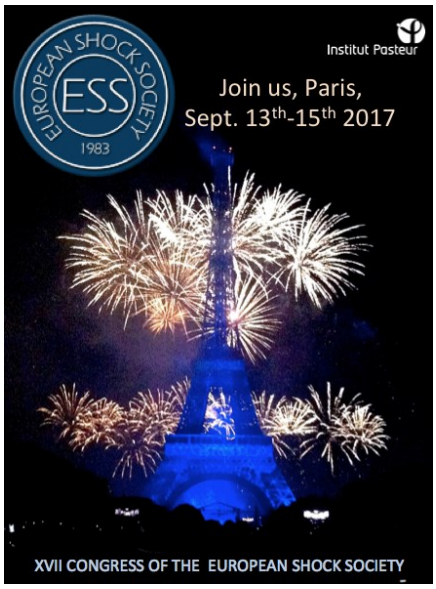
Present status of the upcoming ESS Congress (2017)

Institut Pasteur will host the 17th Congress of the European Shock Society



Institut Pasteur, Paris, was founded in 1887 following an international appeal for funds, and opened on November 14, 1888. The aims were (i) public health, welcoming outpatients for rabies vaccination, (ii) research in microbiology and (iii) teaching. At its launch, there were five research units led by:
Emile Duclaux for General Microbiology, Charles Chamberland for Microbiology applied to hygiene, Elie Mechnikoff, in charge of Morphological microbiology, Joseph Grancher, MD, led the Rabies department, Emile Roux, MD, was head of Technical microbiology.


L' Institut Pasteur en 1888

Soon thereafter, Louis Pasteur sent scientists throughout the world and in 1891, Albert Calmette opened the first Institut Pasteur abroad in Saigon (Vietnam) where he studied vaccines against smallpox and rabies. In 1894, Yersin was sent in Hong Kong where he discovered the plague bacillus and created a laboratory in Nha-Trang. Nowadays, the International Institut Pasteur Network comprises 33 institutions worldwide, they are present on every continent (almost 23,000 people).

Ten Nobel prizes have been awarded to Pasteurians: **1907**, Alphonse Laveran *(Plasmodium falciparum);* **1908***,* Elie Metchnikoff *(Phagocytosis);* **1919***,* Jules Bordet *(Complement);* **1928**, Charles Nicolle *(Typhus);* **1957**, Daniel Bovet *(Anti-histaminic);* **1965**, François Jacob, Jacques Monod, André Lwoff *(genetic control of bacterial enzyme synthesis);* **2008**, Françoise Barré-Sinoussi and Luc Montagner *(HIV).*

Nowadays, Institut Pasteur, Paris hosts 130 research units gathered in 11 departments, 14 technologic platforms, 15 national reference centers, a medical center (> 90 000 vaccinations) and welcomes 500 students from 60 different countries.

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Our ESS congress will be held in the Center for Scientific Information (CIS), built and opened in 1994 thanks to the generosity of the Duchess of Windsor. The CIS houses an auditorium (maximum capacity: 529 people) close to two halls (285 m^2 and 200 m^2) designed to greet delegates and guests and hold coffee breaks, poster sessions, exhibitions and cocktail receptions.

Jean-Marc Cavaillon

Introducing ESS research groups:

Bridging Shock, Trauma and Sepsis towards the Clinic - Translational Research Group around Markus Huber-Lang

Within the last decade, shock, trauma and sepsis research has become a crucial pillar at the University of Ulm, Germany, driven by a group around a trauma-surgeon. After completing medical school and his first clinical training at the University of Freiburg, Germany, Markus Huber-Lang joined Peter Ward's lab at the University of Michigan, USA, for a postdoc-fellowship between 1998–2000, where he investigated the role of complement in acute lung injury, sepsis and multiple organ failure, finding various detrimental effects of both activated complement and neutrophils.

Markus Huber-Lang then "squared the circle" as clinician and researcher by receiving training and working as a general and trauma surgeon side by side with translational research activities and building a trauma lab together with two clinical colleagues. His young team was subsequently funded by the Emmy Noether excellence program (by the German Research Foundation) with a focus on innate immune dysfunction after tissue trauma and during sepsis, where several involved pathways could be described.

In 2010, Markus Huber-Lang became a professor for Clinical and Experimental Trauma-Immunology and the leader of the Research Unit KFO200, addressing the early danger response after trauma. In close collaboration with P. Radermacher, Ulm, and other international experts (H. Redl, S. Bahrami, T. Mollnes, F. Hildebrand, I. Marzi, M. van Griensven, etc.), the Huber-Lang group has investigated the intensive cross-talk of defense systems and the coagulation cascade as well as organ-blood barrier dysfunctions during sepsis and multiple organ failure. Moreover, the group has recently addressed the role of innate immunity in fracture healing and regenerative processes in close collaboration with A. Ignatius, Ulm University. As speaker of the German trauma research network

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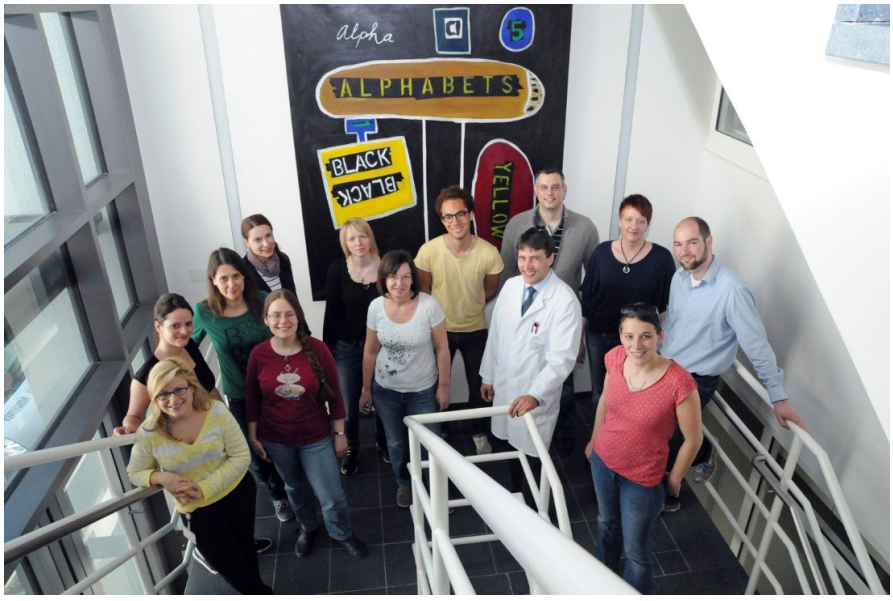
(NTF), Huber-Lang has set up a nationwide biobank for sera from polytrauma patients in multiple collaborations for common translational research purposes. An overall effort of the Huber-Lang team is to bridge the lab's findings and clinical reality in acute critical illnesses (including hemorrhagic shock, polytrauma, sepsis and multi-organ dysfunction) for a reliable immune-monitoring of patients. The final aim of the team effort is to find effective immune-modulatory approaches to improve the (surgical) management of critically ill patients and their outcome.

ESS-members of the lab are: Rebecca Wiegner, Stephanie Denk, and Annette Palmer
Direct contact can be made by e-mail: markus.huber-lang@uniklinik-ulm.de.

Visitors are always welcome; we are located close to the Alps and Austria, less than 4 hours travel from Italy. In August, we will (nearly) all be by the Mediterranean Sea, so that time is dedicated to relaxation and philosophizing on how to live and to become resilient against shock, trauma and sepsis.



Currently, the Huber-Lang group has almost a dozen members plus students. Daniel Rittirsch and Michael Flierl, two of Huber-Lang's first students, have meanwhile established their own group. Recently, the doctorial student Stephanie Denk (left) has won the ESS New Investigator Award.

Markus Huber-Lang

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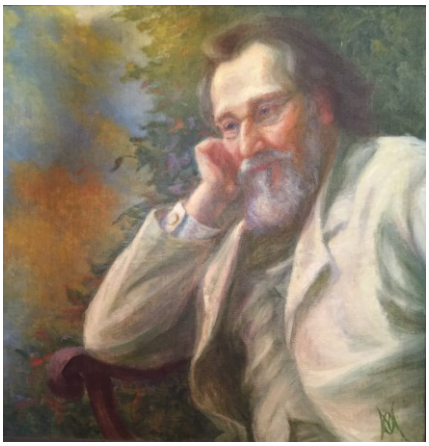
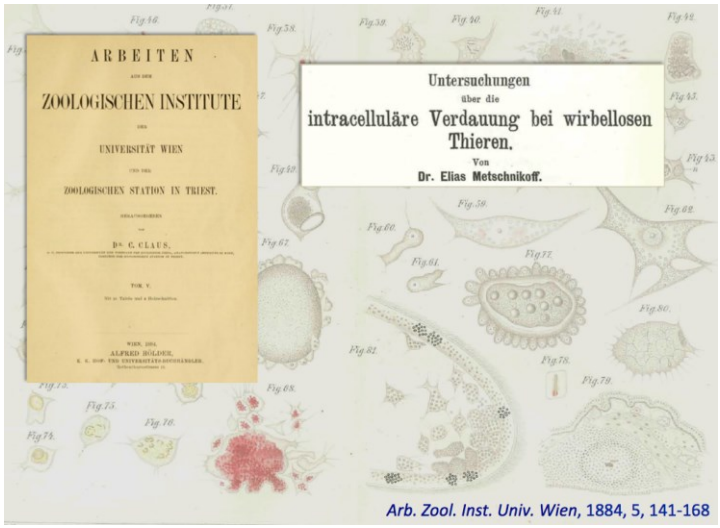
The centenary of the death of Elie Metchnikoff (1916 – 2016)



In 2016, we are celebrating the death of Elie Metchnikoff who passed away on July, 15th, 1916. Metchnikoff is one of the most fascinating and prominent scientist of his time. Educated as an embryologist, he was initially interested by the capacity of cells to perform digestion till he understood the process of phagocytosis with his fundamental discovery made in Messina (Sicily) in 1882. This observation was published in the journal of his friend Carl Friedrich Wilhelm Claus (1835 – 1899), a German zoologist, Prof. of zoology.

Portrait of Metchnikoff, The Pauls Stradins Museum of the History of Medicine in Riga, Latvia

Not only Metchnikoff is recognized as the father of innate cellular immunity, but also, after he joined the Institut Pasteur in 1888 and worked there for the next 28 years, he made other major contributions in the field of ageing. Accordingly, he is also considered as the father of gerontology. To limit the deleterious effect of putrescent bacteria within the gut (which, he thought, were the cause of ageing and senility), he suggested the use of sour milk and yoghourt, and, accordingly, he is considered as the father of the probiotics as well.



Amazingly, he worked on more than 30 animal species, studying inflammation (in guinea pigs, rats, frogs…), infectious diseases (in monkeys, caimans, gooses…), ageing (in parrots, dogs, humans…), gut microbiota (in bats, nandou, cats, horses, birds…), obtained germ free animals (tadpoles, flies, chicks), and proposed hypotheses to understand age-associated senility (in rabbits, humans…). [of note, only rarely in mice… this may be why he was so successful ;-)]. Metchnikoff was a fantastic teacher, and a walking encyclopedia, and welcomed more than 100 trainees from all around the world. One of them received later the Nobel Prize for his work on complement (Jules Bordet). Alexandre Besredka, his successor got the first ever obtained anti-endotoxin antibody. Metchnikoff wrote books on immunity, on inflammation and on philosophy; he was a true giant of science.

Jean-Marc Cavaillon

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Back to the historical roots:

Interview with one of the founders of ESS (Sándor Nagy, Hungary)

Dr. Nagy received his MD from the University of Szeged and his PhD from the Hungarian Academy of Sciences. He began his research career in 1957 in the Pathophysiology Institute and joined the staff of the Institute of Surgical Research of Szeged University in 1960. He has been affiliated with this Institute ever since. He had been director for 13 years and currently he is professor emeritus.

He is a founding member of the European Shock Society and had been vice president for 11 years and served on the editorial board of its journals for two decades. He had been an officer in the Hungarian Societies of Surgery and Physiology. His research interests are surgical pathophysiology and circulatory shock. He has published more than 200 papers in these fields including 2 papers in Nature and several publications in Circulatory Shock and Shock.

What prior events have led to your invitation to the inauguration meeting of the European Shock Society?

In early 1983, I got a letter from David Lewis about his plan to establish a society in Europe with a similar profile to that of the already 5-year old Shock Society in the US. I knew David for more than 15 years by that time. He graduated as an MD at Columbia University in New York where he also earned his PhD degree and conducted research in the field of surgical pathophysiology. After his marriage, he moved to Sweden, where he used to work in Lund and Malmö and was employed at Linköping University at the time of the establishment of the Society. We had first met at a conference in Budapest in 1967 and then at another congress in Göteborg in 1968 and later at several meetings in the 70'-s. Asking for reprints of scientific papers was very common in those times and was another tie between us. Financial support of my travel costs for the inaugural meeting was also arranged by him and was provided by the Ferring AB Company on his recommendation (there were very limited funds available for traveling abroad for non-party members in the communist countries).

How was the inauguration meeting organized?

The inauguration/constitutional meeting which was called together by David Lewis (for the 15-17th of April, 1983) had two major aims: firstly, to present the status and results of the actually running shock research projects in Europe and secondly, to establish the European Shock Society (ESS). The lectures of this meeting were published in one of the regular issues of the Ferntström Foundation Series entitled „Shock Research". The constitution document and the bylaws were also approved at this meeting. David Lewis suggested that we elect an executive committee recommending himself as the past-president. I highly appreciated this humble action from him and feel the same ever since. Ian Ledingham, a British surgeon was elected as president and 3 regional vice presidents were

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also elected: Jean-Louis Vincent, Gian Paolo Novelli and me (as a representative of Eastern Europe). I have fulfilled this duty for 11 years.

What was the official journal of the society?

The necessity of an own journal has already arisen during the constitutional meeting. The organizers have invited a representative of the publisher of the journal „Resuscitation" and it was suggested that the society adopt this as its official journal, but owing to its relatively limited and narrow scope, this suggestion was not supported by the Committee. The next congress was organized in Manchester in 1984 (a photo was also taken of the executive committee during this meeting, see below). By this time, an agreement was reached with the American society that they give positions to the ESS in the editorial board of Circulatory Shock. Rod Little was elected as a regional (European) editor and, among others, Konrad Messmer from Germany and me from Hungary were delegated as members of the Editorial Board. I served my duty at this journal from the 1st of January, 1985 until its termination in 1994; when the publisher decided not to publish Circulatory Shock (under this name) any longer because of the low level of profitability of the journal. The official successor is the Shock journal where I continued with the editorial board member duties; I served the two journals altogether for nearly 20 years (until August 2004).

Founding members of the ESS (photo was taken in Manchester in 1984
Sitting row (left to right): Lewis, Messmer, Ledingham, Haglund
standing row (left to right): Vincent, Little, Nagy, Novelli

What further important meetings can you remember?

I have regularly attended several ESS congresses and also Shock Forums that were organized by Günther Schlag in Vienna (starting in 1986). The first joint meeting with the Shock Society was the World Shock Congress organized in 1987 in Montreal, where in addition to our Society, the newly established Japanese and Brazilian Shock Societies also participated. Besides ESS congresses, I also

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attended meetings of the European Society for Surgical Research (ESSR). Once (May 2-5, 1988) a joint meeting with the participation of the ESS and ESSR also took place in Bologna; this was organized by Konrad Messmer (who also served as the chief editor of the official journal of that society: European Surgical Research). I met David Lewis also at an ESSR conference in Warsaw. I also remember an ESS congress organized by Ulf Haglund in 1994 in Stockholm.

What other memories can you recall from the founding members and whom did you have contact with later on?

David Lewis was a jovial, benevolent, friendly person with always high spirits. Since I formerly also spent a year in the US, we often had conversations about America. Nonetheless, I have to mention that he really liked Europe and he became a real European he was an American-turned-Swede I think. In the 90's, he also visited us in Szeged with a plan to establish a Swedish-Hungarian scientific cooperation. As for others, I have known Jim Parratt for a long time by that time and our friendship continued ever since. I had scientific cooperation with Konrad Messmer; many of my colleagues visited his institute in Munich. I can also remember the activity and field of interest of several founding members: Ansgar Aasen conducted thrombosis/hemostasis research, Sven-Erik Bergenz, a professor of surgery (as far as I remember) worked at the Lund University and had cooperation also with David, Ulrich Gruber was a surgeon from Basel who was dealing with transfusion problems, Ulf Haglund in 1983 already appeared to be a talented surgeon and gifted experimenter who was also involved in the establishment of the Society (helping David) and became the secretary; he worked as a professor of surgery in Uppsala later on. Bert Thijs also organized an ESS congress later. Jean-Louis Vincent was an intensivist with excellent publications and clinical trials later. Rod Little was the first treasurer and a later president of the Society and an Associate Editor of Shock. I met Jarle Vaage here for the first time and we also met in Montreal later. Later, we established a very fruitful cooperation resulting in many scientific publications. He worked at the Karolinska Institute for a while, but later he returned to Norway and became the president of the Scandinavian Society of Thoracic Surgeons.

reported by Andrea Szabó

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Journal Club: What is new in shock research?

Highlights of remarkable findings recently published in shock research

Sepsis, immune status, patients

Source: Irina N. Shalova *et al.* Human monocytes undergo functional reprogrammingduring sepsis mediated by hypoxia-inducible factor-1α. **Immunity.** 2015 Mar 17;42(3):484-98. (link to open access paper)

Main important messages:

→ Altered immune function of monocytes during sepsis is NOT A GLOBAL defect.

It is known for more than 25 years that monocytes from sepsis patients display an altered *ex vivo* cytokine production (*Munoz et al. J. Clin. Invest. 1991, 88, 1747*). In contrast, the group of Subhra Biswas (Singapore) demonstrates that monocytes from sepsis patients may display certain enhanced immune function, such as phagocytosis, anti-microbial activity, metaloproteinase-9 & 19 mRNA expression or VEGF release.

→ IRAK-M expression is controlled by HIF-1α

The team of Eduardo López-Collazo (Madrid) had found that IRAK-M was up-regulated in monocytes of sepsis patients and was partially responsible of the altered cytokine production (*Escoll et al. Biochem Biophys Res Commun. 2003; 311, 465*). Biswas' team elegantly demonstrated with siRNA that HIF1α subunit of the heterodimeric transcription factor "hypoxia-inducible factor-1, is favoring the expression of IKAK-M.

Written by: Jean-Marc Cavaillon, Institut Pasteur Paris

Sepsis, biomarkers

Source: McHugh *et al.* A molecular host response assay to discriminate between sepsis and infection-negative systemic inflammation in critically ill patients: discovery and validation in independent cohorts. **PloS Med**, 2015, 12, e1001916 (link to open access paper)

Main important messages:

→ Gene expression can help to identify patients with sepsis

A four-gene classifier combining *CEACAM4, LAMP1, PLA2G7*, and *PLAC8* RNA biomarkers (SeptiCyte Lab) studied in 5 cohorts of patients (n=345) offers a promising approach to identify patients with sepsis. AUC varied from 0.85 to 0.95 depending on the cohorts.

SeptiCyte Lab was significantly better at differentiating cases from controls than all tested parameters, including clinical ones and procalcitonin in all tested cohorts.

Written by: Jean-Marc Cavaillon, Institut Pasteur Paris

Oxygen, hemorrhagic shock, sepsis

Source: Rahat MA *et al.* Oxygen mitigates the inflammatory response in a model of hemorrhage and zymosan-induced inflammation. **Shock** 2016 Vol 45 No2 pp. 198-208 (link to abstract)

Short summary: This recently published article by Rahat et al. from the Immunology Research Unit at Carmel Medical Center, Haifa, Israel provides strong evidence that intermittent oxygen significantly improves the pro-anti-inflammatory immune balance, dramatically reduces the macrophage influx to the inflammatory site and overall improves mid-term survival in a double hit murine model of hemorrhagic shock and zymosan-induced peritonitis. The well-described protocol for intermittent oxygen application was adjusted just below the toxic threshold of oxygen. In accordance, a recent report also indicated that an early short term (2 x 3 hours) exposure of 100% oxygen was capable to abolish the impairment of fracture

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healing after thoracic trauma (Kemmler et al. PlosONe 2015). It is noteworthy that present study found only a limited effect of oxygen on pro-inflammatory cytokine profiles at the local site but a marked suppression systemically.

In conclusion, oxygen may ameliorate the systemic inflammatory response post trauma.
In the future, it will be utmost interesting to see whether translational clinical studies will support the idea of oxygen as an effective drug for treatment of post traumatic complications, such as development of sepsis and multi-organ failure after trauma.

Written by: Markus Huber-Lang, University of Ulm

Regulation of inflammation, inflammasome, signaling, TLR4, interleukin-1β, species differences

Source: Moritz M *et al.* Human Monocytes Engage an Alternative Inflammasome Pathway. **Immunity.** 2016 (link to abstract)

Short summary: It is generally accepted that the inflammasome activation requires two signals for IL-1β maturation. The first signal e.g. lipopolysaccharide (LPS) recognition via Toll-like receptor (TLR), induces the transcriptional upregulation of IL-1β, while the second signal activates the inflammasome complex. On the other hand, more recently, a direct sensing of LPS by caspase-11 or its human orthologs caspase-4 and caspase-5 in the cytosol has been shown to activate the NLRP3 inflammasome and trigger cell death. Here, the term „non-canonical inflammasome“ next to the previously described „canonical“ inflammasome was introduced.

While the two-step (two stimuli) activation mechanism for the NLRP3 inflammasome with subsequent IL-1β maturation was confirmed in the murine system, in freshly isolated human monocytes IL-1β was produced in response to a single signal, acting via TLR4, contradicting the two-step activation dogma. In light of the fact that no established human monocyte-like cell line reacts to this signal, in the present work, Hornung et al. utilized the newly developed human monocyte-like cell culture system in order to understand the basis for the species difference. At the genetic level, the authors have identified the components responsible for signal transmission to, and activation of the NLRP3 inflammasome. Unlike classical (canonical) NLRP3 inflammasome signaling, this inflammasome activation termed “alternative inflammasome” by the authors, proceeds independently of potassium efflux, pyroptosome formation, and pyroptosis, while it engages TLR4-TRIF-RIPK1-FADD-CASP8 upstream of NLRP3.

Hornung and colleagues show that this new alternative pathway explains why human monocytes do not require a second signal to secrete IL-1β. Interestingly, in mouse monocytes this pathway is not activated, again explaining why a second stimulus is necessary in mice. Furthermore, while the inflammasome activation in mice was accompanied by programmed inflammatory cells death, this phenomenon was not observed in human cells after activation of the alternative inflammasome. Taken together, the new data indicate that this alternative inflammasome may play a critical role in inflammatory processes in humans, not only due to the pathogene clearance, but also in sterile inflammation conditions, such as atherosclerosis, type 2 diabetes, gout or Alzheimer`s disease.

Conclusions: LPS induces IL-1β maturation and secretion in human and porcine monocytes, but nor in murine monocytes via the so-called “alternative NLRP3 inflammasome” pathway in human monocytes. This previously unknown, alternative inflammasome signaling proceeds independently of potassium efflux or programmed inflammatory cells death (pyroptosome formation and pyroptosis) and is mediated via TLR4-TRIF-RIPK1-FADD-CASP8 upstream of NLRP3.

Written by: Borna Relja, University Hospital Frankfurt

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Mitochondria, sepsis, organ dysfunction, consensus

Source: Arulkumaran N *et al*. Mitochondrial function in sepsis. Shock. 2016 Mar;45(3):271-81 (link to abstract)

Summary: The paper is part of a series of papers addressing the role of four key players in sepsis-induced organ dysfunction (epithelium, endothelium, immune cells, mitochondria).
Arulkumaran *et al*. (on behalf of the Acute Dialysis Quality Initiative (ADQI) XIV Workgroup deal with 5 key questions addressing the function of mitochondria in sepsis-induced organ dysfunction and the underlying molecular mechanisms, the role of the trade-off between cell-adaptive and organ-maladaptive responses and potential mitochondria-based therapeutic options.

Main important messages:

→ Aside from cellular responses, it is of high importance to study regulatory processes on a subcellular level

→ Mitochondria are very complex organelles and their exact role in inflammatory processes depends on the studied time point, species and organ as well as on the severity of illness

→ Since mitochondria are involved in multiple functions (e.g. metabolism, signaling, injury, repair (fission and fusion, mitophagy, biogenesis)) their role in organ dysfunction can be "the good, the bad or the innocent" → The chicken-egg dilemma continues

This outstanding review provides many insights that will help to extent the research on (early) diagnostic and treatment opportunities in sepsis.

Written by: Inge Bauer, University Hospital Duesseldorf

Transcriptomic profile of immune response in sepsis, gene expression, immunity

Source: Emma E Davenport *et al.* Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Lancet Respiratory Medicine. 2016 Feb 22. pii: S2213-2600(16)00046-1 (link to open access paper)

Main important messages:

→ Sepsis patients with community-acquired pneumonia (CAP) can be divided into two main groups regarding their pattern of the whole genome transcription in their circulating leukocytes. Patients reacting by expression of 'sepsis response signatures 1' (SRS1) had higher mortality and this signature is characterized by immunosuppressive profile (e.g. reduced expression of genes related with T cells activation, antigen presentation) in comparison with another group called SRS2.

→ Importantly, no recorded clinical variable was able to discriminate patients with SRS1 and SRS2. Another striking finding was that the type of septic response was independent of the timing of sampling revealing that the immunosuppressive phenotype occurs independently of the time from sepsis onset.

→ The authors also tried to find relationship between the patient`s genetic heterogeneity and the type of SRS they present. To achieve this, they looked for disease-specific eQTL (expression quantitative trait loci, loci that can influence the level of gene expression. An attempt was also made to search for SRS-specific eQTL. Many sepsis-related eQTL were differentially overrepresented in specific pathways containing genes characterizing SRS1 or SRS2. They included hypoxia inducible transcription factors HIF1A (HIF1α) and EPAS1 (upregulated in SRS1) and MTOR (downregulated in SRS1).

This observations imply that transcriptome profiling could be the initial part of the personalized medicine approach in sepsis.

Written by: Tomasz Skirecki, Center of Postgraduate Medical Education, Warsaw

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Journal Club Special:

Sepsis-3: a fundamental upgrade or yet another (confusing) twist on the sepsis front?

The 2016 February issue of the Journal of American Medical Association (JAMA) published a series of three papers under an acronym "Sepsis-3" (1-3). These publications finalize the long awaited effort taken up by a team of 19 international experts in the field of sepsis, some of whom are members of the international Shock Societies family. The main goal of this effort was to update the existing definitions related to the perception and diagnosis of sepsis syndromes based on a more in-depth understanding of the older and more recent scientific evidence. From Honolulu (45th Critical Care Congress) to Brussels (36th ESICEM symposium), separate sessions were devoted to explain the new guidelines/definitions and related influences as well as uncertainties their adaptation is expected to bring (watch an exemplary 1h SCCM/ESICM session at: https://www.youtube.com/watch?v=SIu3rqsAkKo)

What do the new definitions actually bring to the table? If I had to describe it with a single word, it would be "*simplification*". What about two words? Then I choose "*complex simplification*". Upon the first glimpse, however, the new terminology does plenty of good by "cleaning up the act" and eliminating several overlapping and confusing descriptors like sepsis syndromes, severe sepsis, sepsis and septicemia. Undoubtedly, this will make cross-communication and reporting more precise. I refer you to a short and entertaining 3min cartoon video clip produced by JAMA that nicely summarizes the main points of Sepsis-3 (https://www.youtube.com/watch?v=L5xKW--drRg). Those who are ready for a more extreme challenge, i.e., a 6min narration by Derek Angus himself featuring snow white shirt and a killer purple tie with matching hanky, can locate it on YouTube as well*.

Even though viewed as a positive development, the Sepsis-3 will likely create some friction before it gets solid traction in the medical community. Allow me to summarize the selected key points and share my brief personal perspective on some of those.

The things that enter with a bang:

- Organ dysfunction as the main component of the sepsis definition. SOFA and quick (q) SOFA become now key descriptors in defining sepsis, i.e., increase in (q)SOFA ≥2 points + infection (confirmed/suspected) = sepsis.

This is a huge shift; we move away from inflammatory states (see below) to organ failure as the decisive factor. This is not just about the sheer definition anymore; the identification focus shifts to patients more likely to perform poorly (and/or die). In other words, increasing (q)SOFA, not SIRS (see below) is the new alarm bell prompting physicians to consider an infection (and sepsis). I actually like it as this system preferentially picks out those with the highest risk (SIRS discriminates very poorly there). A potential caveat: SOFA is not uniformly used across the EU hospitals and will need to be incorporated into the clinical routine.

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The things that remain anchored:

- Infection – either confirmed or suspected.

Ain't no sepsis w'out them bugs! We all would love to get rid of the "suspected" part but this will not happen until better/more precise detection systems come aboard –maybe at the time of Sepsis-4 update… New SOFAs do not really improve this part.

- Septic shock[#] – the term remains but definition has been somewhat altered.

The things gone with the wind:

- Wave good-bye to severe sepsis and septicemia definitions!

I dare to say they will not be missed by many.

The things you might think are gone but not quite:

- SIRS; the task force has ruled it as inferior/not adequately informative, hence SIRS serves no longer as the key component of defining/diagnosing sepsis.

Be that as it may, I foresee some resistance on this one. Though indeed burdened with low specificity, the "SIRS" term is considered by many physicians as a red warning light that provokes more attention/in-depth diagnostics. In all honesty, the task force did not demonize SIRS; they do admit it may effectively help in spotting an infection. Personally, I see SIRS as a useful tool that in some instances may cover the proverbial "no man's land", i.e., identify an infected patient that has not yet deteriorated by ≥2 SOFA score points (hence short of becoming septic *per definitionem novum*).

- Lactate monitoring[#] – was not officially included given that it does not outperform (q)SOFA as descriptor of risk increase/sepsis severity. Though it looks like the experts might have had a heated debate on this one. Plus you should have seen the critical talk by Konrad Reinhart at ISICEM - part of it focused on the lactate monitoring as well!

Ending, please do not trust me and rest comfortably after reading this piece. There is so much more to the story, a series of unmentioned limitations included. Do get your own angle on those landmark (either in the positive or negative sense) changes. I hope I was able to whet your appetite for more and who knows, maybe to provoke you, dear reader, to write your own opinion piece? Nothing against to disagree with my perspective – isn't the good science precisely about that!?

Marcin Osuchowski

* https://www.youtube.com/watch?v=jjLoyKHHFok&nohtml5=False

[#] too complex to be fully summarized here; please refer to the original publications

References:
1) Singer at al. JAMA. 2016 Feb 23;315(8):801-10 (PMID: 26903338)
2) Seymour et al. JAMA. 2016 Feb 23;315(8):762-74 (PMID: 26903335)
3) Shankar-Hari et al. JAMA. 2016 Feb 23;315(8):775-87 (PMID: 26903336)

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Sepsis and Trauma HEADLINES

- Key note address from ***Achim Steiner*** (Under-Secretary-General of the United Nations, Executive Director of the United Nations Environment Programme and designated new director of the Oxford Martin School) held at the German National Academy of Sciences meeting ***"Sepsis - The Challenges of Science, Politics and Society"***. In his keynote address, he clearly states that tackling sepsis is crucial to more than half of the 17 goals of the 2030 agenda for sustainable development!

  This agenda was adopted by the UN Sustainable Development Summit in September 2015 and aims to end poverty and hunger, improve health and education, make cities more sustainable, combat climate change and protect oceans and forests.

  You can access Achim Steiner's full keynote lecture here: www.unep.org/KeynoteSteiner

- ***World Sepsis Day / Global Sepsis Alliance Open Supporter Meeting*** in Brussels March 16, 2016.

  Please find the minutes as well as all presentations by following this link: https://cloud.med.uni-jena.de/public.php?service=files&t=faaa655a8fa61297d139d2a90cf843e7
  www.world-sepsis-day.org

- ***SEPSIS-3:***

  - Statement on the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) ***Task Force Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)***

  - ***Journal Club***: Marcin Osuchowski: **New sepsis definitions**

The **European Medical Education Initiative for Advanced Bleeding Care in Trauma (ABC-Trauma)** (Chairs: Rolf Rossaint, Aachen, Germany and Donat R. Spahn, Zürich, Switzerland; http://advancedbleedingcare.org/) was formed in 2004.

Very recently, the ESS endorsed the 4th edition of **"The European guideline on management of major bleeding and coagulopathy following trauma".**

We are happy to inform you that the manuscript is now published in Critical Care:

http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1265-x

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Statement on the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM)

Task Force Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

GSA
GLOBAL SEPSIS ALLIANCE

Statement on the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) Task Force Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

The mission of the Global Sepsis Alliance (GSA) is to provide opportunities for and be supportive of global interaction, such that the Global Community might address with equal commitment and vigor the needs of children and adults with sepsis in both the developed and developing world. It aims to provide the ability to speak with one united voice to offer consistent, easily understood messaging to governments, philanthropists and the public, and to easily identify and access resources and people of common purpose and intent within and without the scientific community with the goal of reducing the global burden of sepsis.

With the above mission in mind the GSA welcomes the increased academic interest in sepsis generated in response to the reports of the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) Task Force Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[1-3]

The task force articulated key concepts which the GSA has long promoted as part of its mission including that:

- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs (agreed at the first meeting of the Global Sepsis Alliance at the Merinoff Symposium in New Jersey in 2010).
- Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.
- What differentiates sepsis from uncomplicated infection is the presence of (even minor degrees of) organ dysfunction.
- Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection, in which case the patient has unrecognized sepsis.

The Task Force offered a new definition for sepsis, namely that "Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection" and suggest that organ dysfunction be identified using the Sequential Organ Failure (SOFA) Score rather than the criteria for organ dysfunction previously adopted by the Surviving Sepsis Campaign. The task force concluded that the term severe sepsis was redundant.

In addition, the Task Force sought to evaluate clinical criteria to identify patients with sepsis through the interrogation of large clinical databases in the USA and one hospital in Germany. From this exercise they offered quick SOFA (qSOFA) as a clinical scoring system that identified patients in who infection was assumed (as they had received antibiotics and had microbiological cultures taken) and who were more likely to die or to be treated in an intensive care unit for 3 or more days.

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The task force also articulated existing limitations of their suggested approach and offered key messages that should be emphasized, namely that with regard to qSOFA:

- "The task force strongly encourages prospective validation in multiple US and non-US health care settings to confirm its robustness and potential for incorporation into future iterations of the definitions."

- "Neither qSOFA nor SOFA is intended to be a stand-alone definition of sepsis. It is crucial, therefore, that failure to meet 2 or more qSOFA or SOFA criteria should not lead to a deferral of investigation or treatment of infection or to a delay in any other aspect of care deemed necessary by the treating practitioners."

- The task force also stressed that SIRS criteria still remain useful for the identification of infection.

Although the task force chose not to include measurement of serum lactate in qSOFA, the also stated that "The task force recommendations should not, however, constrain the monitoring of lactate as a guide to therapeutic response or as an indicator of illness severity." Lactate is included in the proposed new definition of septic shock but the Task Force notes that where lactate is not available other indicators of hypoperfusion may be used.

The GSA agrees with these statements, particularly that the proposed definition and qSOFA are derived from data from US hospitals and therefore need external validation before being widely adopted. This further highlights the need to generate sepsis-related data in low and middle income countries and prospectively test the definition widely around the world. Indeed, advocating for data from low and middle income countries is a mandate of the GSA. A change in SOFA score, being reliant on a laboratory services, will not be practicable as a diagnostic criterion in many locations in LMICs. The GSA proposes that governments, agencies and organizations such as the World Health Organization be engaged in devising and testing surrogate measures for such regions by way of 'operationalizing' the academic definitions.

We, like the authors, also recognize that improving on definitions is an iterative process and further refinement and changes may prove necessary. Thus pending prospective testing, the decision of how hospitals, health care systems and countries respond to the task force recommendations rests with those individual hospitals, health care systems and countries.

K. Reinhart	N. Kissoon	R. Daniels	S. Finfer	R. Schachter
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References

1. Singer M, Deutschman CS, Seymour C. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801-810.

2. Seymour CW, Liu VX, Iwashyna TJ. Assessment of clinical criteria for sepsis: For the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):762-774.

3. Shankar-Hari M, Phillips GS, Levy ML. Developing a new definition and assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):775-787.

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The global Shock family meets again: 2016 IFSS Congress in Tokyo

In October 3-5 of this year, our colleagues from the Japan Shock Society under the leadership of Professors Hiroyuki Hirasawa (current IFSS President) Shigeto Oda and Masao Miyashita, will organize and host the upcoming Congress of the International Federation of Shock Societies. Japan's capital city with its Tokyo Dome Hotel has been selected as the location; no doubts an attractive and exciting venue! The website is already functional and preliminary program featuring 12 various areas of interest has been recently posted on-line at: http://www.congre.co.jp/ifss2016/index.html. Likewise, the abstract submission process has been already open and you can submit your works until 28 April 2016 (unless an accommodating extension of the deadline is still offered).

The ESS strongly believes that we should try our best to adequately represent Europe in Japan, not only with the purpose of showing our best science but even more importantly, to highlight the lasting and strong camaraderie among the existing Shock siblings of the IFSS. While an official joint session under the ESS/IFSS patronage has been already arranged, we sincerely encourage individual submissions and/or personal participation in Tokyo. Of note, the IFSS organizers provide a total of 15 travel Awards (of up to $1,500 for travel and lodging expenses); they will be awarded to investigators (up to 40 years of age) based on scientific merit of the submitted works and financial need of the authors. It is a without a doubt a great and generous opportunity for younger researchers to make their participation at the congress a reality rather than just an unfulfilled wish. Thus, without further cajoling, let us try to reach a decent headcount in Tokyo, dear sushi loving, ESS members!

Your ESS team

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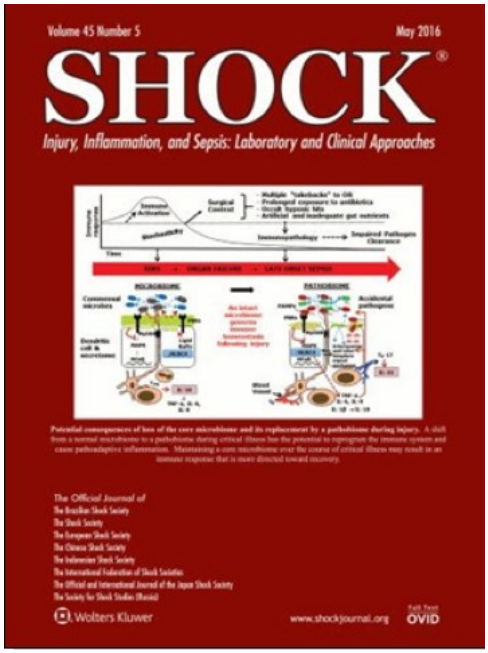
Invitation to publish in Shock®



REMINDER

Shock is a monthly journal that publishes the results of investigations in the field of injury, inflammation and sepsis; of clinical and laboratory origin alike (current IF=3.05). It is the official Journal of all international Shock Societies, including ESS. Thanks to its efficient reviewing process, you will typically have your submitted paper reviewed within 15 days.

So do not hesitate, submit your next best results to SHOCK!

http://www.editorialmanager.com/shock.

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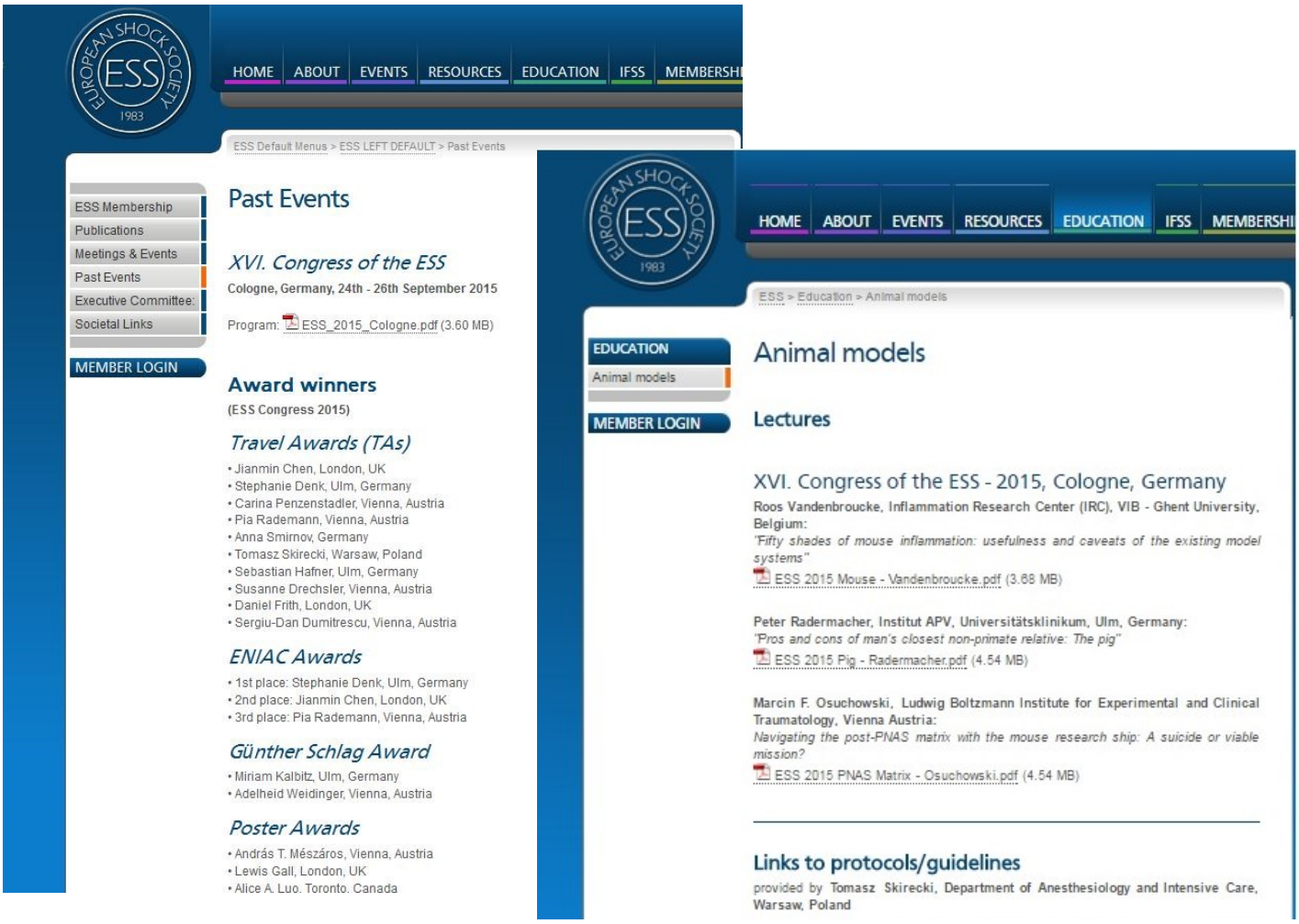
News about our website

We work hard on invigorating different aspects of ESS; recently, we have started expanding our ESS website to make it more attractive and useful to both ESS members and sympathizers. As the first step, we have created two new sites where you can now find historical records from the most recent congress as well as newest relevant info related to selected professional topics - we have focused on pre-clinical research for starters. Program and list of award winners of the ESS 2015 Congress in Cologne are now available at: http://europeanshocksociety.org/PastEvents. Lectures of the „ESS VII: Animal Model to Patient Translation" session of the ESS 2015 Congress together with links to helpful protocols and guidelines related to animal experimentation/modeling are now available at: www.http://europeanshocksociety.org/Animalmodels. This effort will continue and we plan on generating more of such reference/info websites on different specific topics. Remember, we are open for your suggestions and would most sincerely welcome your contribution.

Your ESS team



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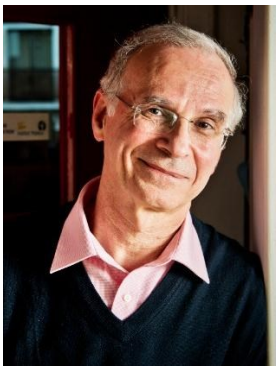

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LAST WORDS ABOUT NEWSLETTER

Dear present ESS member,

If you like your ESS Spring Newsletter, please feel free to share it with your colleagues in the lab, department and/or institute. Perhaps, you could use this opportunity to suggest them to join us (a registration form can be found at the end of this Newsletter). Do not forget that we need you to keep improving our society so it stands proud and strong among other international Shock Societies.

This Newsletter, put together by your peers, belongs to you! We invite you to identify with it as members of the ESS. Moreover, we ask you to help us make it even better. Accordingly, we would be delighted to publish in our next issue any input you might be wishing to share with us (e.g. discussion on a given research/popular science topic, announce available positions in your lab, a contribution to the journal club corner, historical memories, comments about sepsis 3.0 etc.)

Dear past ESS member,

Please do not forget to renew your membership. We need all colleagues, junior and senior alike, to enable the ESS to host in its ranks the best representatives of the European Shock research - at the bedside and/or at bench alike.

Jean-Marc Cavaillon

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European Shock Society

Membership Application Form

Sign up online at **www.europeanshocksociety.org/register**

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