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EDITORIAL

Special Issues of AMR on the Occasion of the 85th Birthday of Harold M. Swartz (HMS): Overview of Part 2 Articles and HMS' Citations on Magnetic Resonance

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1 Special Acknowledgements from Harold M. Swartz for These Special Issues

I am extremely proud and grateful that so many outstanding scientists have contributed to this special issue highlighting the contributions of my laboratory to magnetic resonance, especially in electron paramagnetic resonance. The articles in the two parts of the special issue highlight how advances in both instrumentation and concepts have made EPR of biological systems so productive. This raises my optimism that, where there are current limitations, further technical and scientific progress will make EPR of biological systems even more productive in the future.

While I am of course both proud and humbled by the many senior colleagues with whom I have the privilege of collaborating and exchanging knowledge, I am especially proud of my 'academic children', i.e., those who worked with me in their formative years as students, post-docs, visiting fellows, or young academics in my laboratories. This group includes many very bright and energetic men and women who went on to have very impressive careers, including many who have established their own research groups and produced additional excellent science as well as next-generation scientists. This talented group encompasses Arif Ali, Bill R. Antholine, Goran Bačić, Hal F. Bennett, Rose Caston, Hsiao C. Chan, Eunice Y. Chen, Kai Chen, Ed S. Copeland, Franci Demsar, Jurek W. Dobrucki, Jeff F. Dunn, W. Scott Enochs, Bernard Gallez, Peter Gast, James Glockner, Fuminori Goda, Peter

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Gutierrez, Xiao-Ming He, Hiroshi Hirata, Huagang Hou, W. Brian Hyslop, Anna Iannone, Akinori Iwasaki, Ron J. Jandacek, Philip James, Lesley A. Jarvis, Li Li Ji, Jingie Jiang, Ching-Sang Lai, K. Jim Liu, Kyo Kobayashi, Steve Leichtweis, Karsten Mäder, Colin Mailer, Minoru Miyake, P.D. (Reef) Morse, Susan Morris, David O. Nettleton, R. Javier Nicolalde, Mark J. Nilges, Julia A. O'Hara, Tomasz Panz, Brian W. Pogue, Fraser Robb, Yasuko S. Sakata, Tadeusz Sarna, Phil E. Schaner, Steve Shen, Toshi Shima, Wilson Schreiber, Jason W. Sidabras, Alex Smirnov, Roger Springett, W. Karol Subczynski, Tamiko Suzuki-Nishimura, Aldo Tomasi, Graham Timmins, Ichiro Yamaguchi, Ben B. Williams, Ron K. Woods, and Luigi Zecca.[1] I bask in the light of their special accomplishments and expertise.

I am especially grateful to the editors of this issue, Ann Flood, Steve Swarts, Murali Krishna, and Bernard Gallez who have worked so hard and diligently. And, of course, I am especially grateful to Ann who has had the leading role in conceptualizing this special issue and guiding it through to its completion, including untold hours of effort to improve the clarity of each manuscript. Most of all, I am grateful to Ann because of the many ways that she has made my personal and professional life so satisfying, including her change in career, after she became emerita as a leading health services researcher, to become an outstanding collaborator for advancing so many of what started as *my* professional interests and making them *our* interests.

I also thank the tremendous help and tolerance of Kev Salikhov and Laila Mosina who have gone way beyond the responsibilities of the editorial guidance for having these issues as part of the AMR, facilitating and guiding at every step of the way to successfully herd the contributors (cat-like) into completing the manuscripts while not departing from rigorous peer review of each manuscript (except for the editorials and my histories which, in the tradition of the Journal, are not peer-reviewed).

2 Manuscripts Included in Part 2 of the Special Issue for Harold M. Swartz' 85th Birthday

Part 2 of the special issue starts with four manuscripts which present historical overviews of Harold M. Swartz' (HMS') contributions to magnetic resonance. The initial histories are authored by HMS and present a detailed overview of his laboratories' efforts in three areas of magnetic resonance: (1) free radicals and paramagnetic metals in biological systems and associated EPR instrumental developments advancing in vivo measurements, (2) biodosimetry, particularly focused on using EPR to assess dose in large-scale emergencies, and (3) oximetry, particularly focusing on improving medical decision-making where hypoxia plays a key role in therapeutic success. The fourth historical overview/review is authored by Tadeusz Sarna and colleagues, and focuses on the contributions of EPR and its important implications for understanding melanins and their biological interactions. It particularly focuses

[1] My profound apologies if I have omitted anyone who should be included in this section or the histories.

on the important and complex area of the interactions of melanin with metals and how these impact the potential cytotoxic effects of metal ions.

The next four articles present recent developments in in vivo EPR instrumental developments. Wilson Schreiber et al. describe the major modifications that were made to in vivo EPR to make the instruments better suited to the needs of both the intended *end-use* (for in vivo dosimetry and oximetry) and the *end-users* (who need to have reliable and clinically relevant data available quickly and well integrated into clinical workflow including being operated by available technicians). Sergei Petryakov et al. report on the development of surface resonators used with low-frequency continuous wave in vivo EPR. These resonators have the flexible cables needed to conveniently attach the detection loop to the skin surface and the high sensitivity needed to avoid SRN problems associated with subject motion during in vivo measurements. Hiroshi Hirata and Harold Swartz review resonator developments in three contexts: preclinical oximetry and free radical measurements in small rodents, clinical (human) oximetry, and human dosimetry. They discuss guidelines for developing and optimizing resonators for each of these specific preclinical and clinical applications. Finally, Jim Hyde and his colleagues discuss their hypothesis that, with low Q-value sample resonators, dispersion EPR can provide better signal to noise. To achieve this, high microwave power is needed, and this is problematic for these samples. They found that the primary source of noise is phase noise at the receiver from leakage of microwave through the circulator. Their paper then focuses on the design of reflector bridges with the goal of minimizing this source of noise.

The next group of articles discusses the physical underpinnings for advancing EPR, especially in vivo EPR. Jerzy Koziol and Wojciech Froncisz lead off with an analysis of influence of spurious signals on automatic frequency control (AFC) in EPR spectrometers. While the primary source of spurious signals is leakage across the circulator in the microwave bridge, the signals reflected from the connectors in the line between the circulator and resonator further modify that signal. They discuss two ways to overcome the potential degradation in performance of the AFC from these spurious signals.

Joseph Kao and colleagues at U. of Maryland in Baltimore and the Eatons' lab at U. of Denver report on the use of EPR lineshapes of nitroxide diradicals and their relationship to spin relaxation because of their importance of their use in structural studies. It had been suggested that the usual maximum distance of 5–6 Å, for their use as a measure of interactions for relaxation enhancement, might be extended to a distance as long as 9 Å if the linker in the diradical were more flexible. Using carefully developed synthetic pathways, they made two dinitroxides with interspin distances of about 9 Å and $J> >A$N, but with more flexible amide and ethylenediamine linkers. They then showed that modulation of dipolar interactions at distances of about 9 Å is not an effective electron spin relaxation mechanism, even for dinitroxides with relatively flexible linkers.

Jay Zweier and colleagues report on methods to increase the speed of EPR imaging with nitroxides. They developed and evaluated the use of fast millisecond scan EPR projection acquisition along with a novel reconstruction algorithm optimized for 3D spatial EPR image reconstruction from a high number of noisy projections. This reconstruction method utilizes the raw image projection data and zero gradient spectrum to account for EPR line shape and hyperfine structure of any given paramagnetic probe, without the need for deconvolution that is poorly suited for high noise data. Using fast-scan EPR imaging with this reconstruction method, they found that, while the approach seems effective, excess noise due to technical limitations of currently available instrumentation limited the gains achievable with the new approach. It is likely that future developments of EPR instrumentation will overcome the problems with noise, and image resolutions approaching 100 μm should be possible.

Alex Smirnov and colleagues present an experimental verification of a prevailing but not yet verified assumption of the use of nitroxides to measure oxygen levels. They measured the effects of molecular oxygen in air and pure oxygen at atmospheric pressure on continuous wave EPR spectra of six structurally different nitroxides. Overall, the data further establish nitroxides as robust EPR molecular probes to measure the product of local oxygen concentration and its translational diffusion coefficient under a wide range of conditions such as pH and electrolyte concentrations.

The last set of articles in this special issue deal with EPR and biodosimetry, focusing on its clinical uses for retrospective biodosimetry after unplanned exposures to ionizing radiation. Beinke and colleagues review the value of biological biodosimetry and EPR spectroscopy for medical management of people experiencing acute radiation syndrome. They conclude that biological biodosimetry (based on molecular biomarkers, especially gene expression analysis) and in vivo EPR represent very promising screening tools for rapid triage dosimetry in early phase diagnostics. They also note that biological biodosimetry can be employed to estimate whole-body dose, while EPR dosimetry on nails, bone, or teeth could be used to determine partial body doses which in combination is very useful for medical management.

Vijay Singh et al. summarize the current state of development of drugs that could be given after exposures to ameliorate the damaging effects of radiation. This paper discusses the importance of determining who has actually received a life-threatening exposure, so that the drugs can be given to the people who need them. It concludes that EPR biodosimetry based on measurements in vivo of fingernails and toenails could be especially valuable, because it provides information about the heterogeneity of the dose as well as its magnitude.

Continuing a long-standing collaboration between groups in Japan and Dartmouth, Nakai et al. show that the often-expressed concern about exposure to sunlight potentially compromising EPR tooth dosimetry is not really limiting. They carefully measured the effect of plausible levels of exposure from sunlight and found that this would not result in a large enough effect to perturb the utility of EPR tooth dosimetry.

The final paper is from a leading group of EPR biodosimetry experts from France and the US reporting on the feasibility of using clipped nails for biodosimetry. Tkatchenko et al. investigated the well-known problem that the EPR signal induced by clipping overlaps with the signal induced by radiation, thereby confounding the interpretation of source of the signal. While other techniques like soaking nails have been investigated to try to overcome this problem, this team analyzed the EPR characteristics of the potentially confounding background signal versus the radiation-induced signal. They concluded that it is very unlikely that EPR spectroscopic techniques can be utilized to remove the influence of the background signal for clipped nails.

3 H.M. Swartz' Citations in Magnetic Resonance

The numbers in this listing of HMS' citations have been used consistently throughout all three histories of EPR studies from the H.M. Swartz laboratories: Part 1—free radicals and instrumental developments of in vivo EPR, Part 2—biodosimetry, and Part 3—oximetry. The numbers are derived from the curriculum vita for Harold M. Swartz. While the overwhelming majority of his publications are related to magnetic resonance (and thus included in the histories), some deal with his other professional interests, most notably related to medical education. Consequently, some numbers are skipped in this listing, because references not included in these histories have been removed.

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Author contributions Ann Flood served as the overall lead guest editor for this *festschrift*. Steve Swarts served as the lead guest editor for all articles on which Ann or Hal Harold Swartz were coauthors; Steve was the topic guest editor for dosimetry-related articles. Murali Krishna was the topic guest editor for free radicals and EPR instrumental developments, and Bernard Gallez served as topic guest editor for oximetry-related articles.