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CONTRIBUTION OF HAROLD M. SWARTZ TO *IN VIVO* EPR AND EPR DOSIMETRY

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In 2015, we are celebrating half a century of research in the application of Electron Paramagnetic Resonance (EPR) as a biodosimetry tool to evaluate the dose received by irradiated people. During the EPR Biodose 2015 meeting, a special session was organized to acknowledge the pioneering contribution of Harold M. (Hal) Swartz in the field. The article summarizes his main contribution in physiology and medicine. Four emerging themes have been pursued continuously along his career since its beginning: (1) radiation biology; (2) oxygen and oxidation; (3) measuring physiology *in vivo*; and (4) application of these measurements in clinical medicine. The common feature among all these different subjects has been the use of magnetic resonance techniques, especially EPR. In this article, you will find an impressionist portrait of Hal Swartz with the description of the 'making of' this pioneer, a time-line perspective on his career with the creation of three National Institutes of Health-funded EPR centers, a topic-oriented perspective on his career with a description of his major contributions to Science, his role as a mentor and his influence on his academic children, his active role as founder of scientific societies and organizer of scientific meetings, and the well-deserved international recognition received so far.

FOREWORD

In 2015, we are celebrating half a century of research in the application of Electron Paramagnetic Resonance (EPR) as a biodosimetry tool to evaluate the dose received by irradiated people. The story of development of EPR biodosimetry and *in vivo* EPR is intimately linked to the story of Hal Swartz. During the EPR Biodose 2015 meeting, a special session was organized to acknowledge the pioneering contribution of Harold M. (Hal) Swartz in the field. In the present article, I have tried to portray my previous post-doc director and highlight his main contribution in science and medicine. It is actually a difficult task to portray this fascinating but complex person. To take a comparison in the field of clinical imaging, how to give all pertinent information in a single picture? Actually, it is virtually impossible to describe one tissue with its anatomy, function, metabolic pattern and gene profile in one scan. In the same way, it appeared to me that it was virtually impossible to 'lock' Hal Swartz in one portrait. Therefore, I decided to portray him as an impressionist painting. Impressionists used short, 'broken' brush strokes of pure and unmixed color, not smoothly blended. You may enjoy their paintings piece by piece. You may start by one part or another. Your view of some parts of the painting may differ and depend on the light you shed on the picture. Finally, after having discovered every part in its complexity and from different angles, the real view will come from a long-distance examination. Here, the reader may start with his favorite or a priori knowledge of Hal Swartz, and continue the tour. I did not try to put together a 'unified' story of this scientist. But overall, what you did know about him and what you will learn should finally fuse into a quite realistic portray of Hal Swartz.

FAMILY OF HAL SWARTZ

Hal Swartz was born on June 22, 1935 in Chicago. His father was a chemist (he had wanted to go to medical school, but a combination of lack of money and anti-semitism made that impossible), while his mother was a homemaker initially and later, an office manager. Hal has two sisters. Hal spent all his childhood (Figure 1) in Chicago. His favorite leisure during the childhood was sports, especially baseball (playing and watching the Chicago Cubs), and taking polls on sporting activities (which led to his first publications—the sports editor of the Chicago Sun-Times was taken by the polling activities of Hal and his best friend Ned, ages 10–11 years, and published their results in his column. Hal got married in 1956 and had two children from this first marriage. On September 1st 1982, he married Ann Flood. Along with Ann, he got two additional children, ages 11 and 14 years, which illustrated that he must have loved Ann very much to take on a teenager and preteen! From the four children they now have 05 grandchildren. Hal and Ann share a mutual passion for bird-watching, travel, frogs, single malt whiskey and having whimsical and sometimes weird (inanimate) objects in their house. This couple is particularly cultured and welcoming, characteristics that are definitely

appreciated by the multi-cultural and international researchers they are meeting every day.

Hal and Ann are also able to organize big and spectacular parties that family and friends can really enjoy. There was no scientific meeting organized by Hal without a great party in his garden. Each spring, Hal and Ann are preparing a large amount of exquisite maple syrup. An example of their mutual humoristic quality is their common publication in the Journal of Irreproducible Results[1]. Hal and Ann are also tireless travelers who have visited all over the world. This had allowed Hal to satisfy his major hobby, bird watching (Figure 2). Hal Swartz often says: '*My real job is to do bird watching, my hobby is to do research*'. No scientist can ignore that passion, because in his scientific presentations, Hal is actually putting a picture of bird each two slides! Other hobbies of Hal include watching base-ball games (he is a fan of Chicago Cubs)[2], and of course, making maple syrup. Very importantly, the main qualities of his character, i.e. his conviviality, his curiosity, his willingness to discover things by himself and his outstanding enthusiasm have had a profound impact on his research.

Figure 1. Harold M. Swartz during his childhood.

HIS TRAINING: THE 'MAKING OF' A PIONEER

The way that led Hal Swartz to Electron Paramagnetic Resonance (EPR) and to his biological interests has not been straightforward. Great teaching and self-learning in various fields have shaped his mind to be able to address concomitantly biological and physical problems. He never finished high school (moving to the University of Chicago after 10th grade). From 1951 to 1953, Hal Swartz has had a university education at the University of Chicago (he never graduated from college either, adding 2 years at Loyola to be eligible for medical school but not completing the requirements for a degree). He considered the time at the University of Chicago his best learning education. He liked very much to learn general principles, and was fascinated by the physics and chemistry. He learned a lot by individual reading, often going back to the original papers (i.e. those of Lavoisier). From 1953 to 1955, he attended Loyola University of Chicago. At that time, he made his first research experiments in biology (even at home, where he terrorized his mother with his experiments with fruit flies, which often escaped to roam about the house). He earned his MD degree in 1959 from the University of Illinois College of Medicine. During his second and third year of MD education, he got involved in research on diets. At the end of the medical school, Hal took a rotating internship at the Michael Reese Hospital (1959–1960). During this period, he took additional courses to learn calculus to better understand biophysics. According to him, he got tired of hearing that '*everything should be explained by calculus*'. At the end of the internship, he went to the army (1961–1970). After viewing training films on the effect of radiation on troops, he asked about where they got that information and was told about the special education programs the army had in that field and applied and was accepted for training sponsored by the military in radiation biology at the

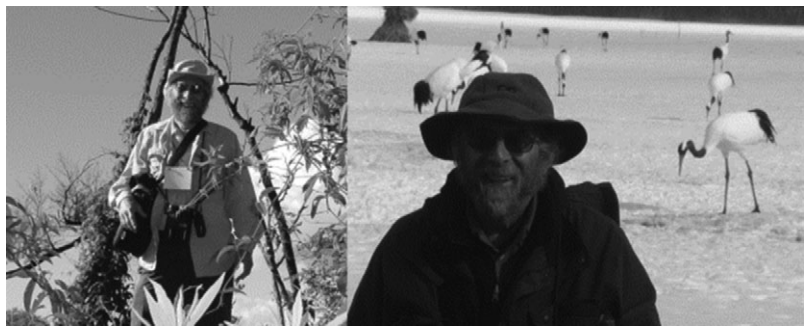

Figure 2. Hal Swartz doing bird watching under very different climates.

University of North Carolina (Chapel Hill) from 1961 to 1962. He liked very much this education period because he was challenged with another student to answer problems of radiation physics, problems that were even not described correctly in the textbooks. He was fascinated by the book of R.D. Evans, 'the Atomic Nucleus'. He then moved to the Walter Reed Army Institute of Research. He was supposed to rotate through various different laboratories. However, he actually remained in the first one, where he had his first contact in September 1961 with an EPR spectrometer. He worked to try to understand the mechanisms of radioprotection, worked on radioprotective drugs, and tried to correlate radioprotection and free radical production[3]. He met the gap between chemical physics and radioprotection mechanisms by analyzing the structure–activity relationships of radioprotective drugs[4, 5], For his PhD, Hal was enrolled in the Department of Biochemistry at the Georgetown University Medical School. Actually, he had courses in Georgetown, but he continued his research at the Walter Reed Research Army Institute. His PhD research was about the importance of the amount of oxygen necessary for life, a careful balance between physiologic and deleterious effects. He looked to the toxic effects of oxygen, and the counterbalance of this toxicity by mercaptoethylamine[5]. The official director of his thesis was Martin Rubin. But, Hal considered himself as a self-learning researcher. One of the biggest challenges for him was to learn EPR himself, and to apply this technology to biological problems. He tried to meet the gap between physics and biology by writing a book together with Bolton and Borg[6]. For sure, this preoccupation has followed him along his career. Later, he even wrote a paper with his daughter, who had no knowledge in biophysics, to try to make EPR a more popular tool for biological people[7]. In Walter Reed, Hal became the Director of the Department of Biophysics (from 1966 to 1969), and then Head of the Department of Biological Chemistry in 1970. Because of his lack of interest in the activities of the latter, he decided to move to the Medical College of Wisconsin, where he started the story of the EPR centers.

THE CREATION OF THREE EPR CENTERS: A TIMELINE PERSPECTIVE ON HIS CAREER

Along his career, Hal Swartz established three National Institutes of Health (NIH)-funded EPR centers: the first one in Milwaukee, the second one in Urbana, and the third one in Dartmouth. The aim for establishing such centers was to offer the unique opportunity to researchers to have a place to go, to meet experts, and to have access to unique instruments. Many scientists over the world visited one of these centers during their career (see later the section 'Hal Swartz as a mentor'). We may consider that his willingness to create these centers has been the germ of his outstanding career and his international recognition.

Hal Swartz spent 10 years in the Medical College of Wisconsin (Milwaukee, WI) from 1970 to 1980. Initially, he was doing research in the Department of Radiology. In 1974, he met with James Hyde who was considering leaving Varian. Together, they set up the first EPR Center (National Biomedical ESR Center), with the complementary expertise of Hal in biology and Jim in instrumentation (Figure 3).

What came out from this center? The technical developments include a saturation-recovery instrument, highly sensitive low-frequency EPR spectrometers and a range of biomedical applications. But, Hal considers that the most important instrumental advance from this period of time was the start of the 'Polish connection'. The start and development of '*in vivo* EPR' would have been impossible without the arrival of *this treasure of very competent people* (as quoted by Hal Swartz) from the Jagiellonian University (Krakow), who came to USA to design instruments and resonators and carry out cutting edge research with them. The first one was T. Sarna, followed importantly by W. Froncicz in Milwaukee (and many others after that, who continued and expanded even after Hal left Milwaukee), followed by T. Walczak in Urbana and Dartmouth, and P. Lesniewski and others in Dartmouth. At that time, came the first ideas of building a low-frequency EPR to apply EPR in biological systems. The potential value of low frequency EPR (for measurements of metal ions) was initially rejected by the study section for the EPR Center in Milwaukee but Jim and Hal preservered and developed it anyway with the main experimental work done by W. Froncisz. The idea of the loop-gap resonator from W. Froncisz came out

Figure 3. Members of the National Biomedical ESR Center in the Medical College of Wisconsin (Milwaukee) in 1977. Near the arrows, you may recognize H.M. Swartz, J.S. Hyde and T. Sarna.

from these studies[8]. Those familiar with the use of EPR in biological systems may definitely appreciate the unique value of this advance for their today's research. From this period, Hal Swartz modestly considered that the research about free radicals in biology did not go very far and was just the continuation of what was started in Walter Reed. However, we certainly may highlight the progresses done in the EPR characterization of melanin[9–13]. This was the start of a long-term collaboration with T. Sarna[14–18], also coming from the Jagiellonian University (Krakow).

In 1980, Hal Swartz moved to University of Illinois in Urbana. Hal was actually attracted by a great research university that was looking to develop excellent medical scientists by a unique MD/PhD program. At the beginning, he continued his research in collaboration with the Medical College of Wisconsin. Then, he set up a new EPR center together with L. Belford and R. Clarkson. The leading idea in his research at that time was to develop something unique without overlap with MCW. The key topics of his research became: oxygen, *in vivo* and spatial resolution. Even if his interest to oxygen was already present in the early days, Hal started to focus on the unique capabilities of EPR to measure oxygen[19–21] and cellular redox status. His willingness to transpose the capabilities of EPR *in vivo* was greatly facilitated by the starting of the interactions with T. Walczak, an outstanding EPR instrumentalist. Hal was convinced about the possibility to develop functional contrast imaging, and invent the concept of metabolically responsive contrast agents[20, 22–25]. Actually, this concept was nothing else than what people reinvented several years later with the concept of 'smart contrast agents' used in molecular imaging, i.e. contrast materials that are activated or inactivated in the presence of a local tissue factor. This concept of oxygen-dependent imaging and redox-dependent imaging has been continuously developed and is still actively developed for the moment by other EPR groups. Another key development during this period was his interest in bringing spatial resolution in the biological systems. Clearly, this has been facilitated by the interactions with P. Lauterbur who joined the College of Medicine at the University of Illinois at that time. Actually, the EPR center and the magnetic resonance imaging (MRI) system of P. Lauterbur were located next to each other. Thanks these interactions, key developments in EPR imaging systems were carried out during this period[26–33]. Besides the instrumental development of EPR imaging, the close relationship between nuclear magnetic resonance (NMR) and EPR offered a unique opportunity in an original characterization of MRI contrast agents. This topic has been pursued by Hal and his collaborators over the time[34–47].

In 1992, Hal Swartz moved to the Dartmouth Medical School. This move was initially motivated by the recruitment of Ann Flood, his wife, as Professor of Community and Family Medicine by Dartmouth. Hal actually found also an opportunity to move there because of the creation a new Department of Radiology, with a high support for research, and because of the possibility to direct an excellent MD/PhD program. And, as usual, Hal came and created a third EPR center: the EPR Center for the Study of Viable Systems. Somehow, we may consider the 90s in Dartmouth as the mature period for *in vivo* EPR. The author of this scientific biography joined the Swartz lab at this period of time. It was a fantastic period, with outstanding post-docs (most of them created their own EPR centers later; see the section 'Hal Swartz as a mentor'), with a profusion of ideas and many new applications in physiology, physiopathology[43, 48–53], pharmacology[54–56], pharmaceutical technology[57–61], radiation biology[42, 62–64] and toxicology[65–73]. All these developments were greatly facilitated by the identification and the development in his laboratory of solid paramagnetic oxygen sensors possessing a tremendous sensitivity to oxygen[74–77]. With the advent of the 21st century, came a new horizon: clinical EPR. Because of the proximity of a clinical hospital in Dartmouth and the favorable environment of clinicians that Hal convinced about the unique opportunity to transfer EPR into the clinic, his dream from a long time ago[78] is now a reality. Actually, the seminal idea that this was feasible came in collaboration with a post-doc from Japan, F. Goda, and their first human experiment was done in 1993 on the arm of a young man bearing a tattoo[79]. The paramagnetic centers contained in the ink were responsible for an EPR signal that was dependent on the perfusion of his limb. Hal stimulated an incredible amount of efforts in his lab for instrumental developments that could be adapted for the clinical situation[80–83]. He also stimulated extensive collaborations on that project to improve the sensitivity and the stability of responsiveness of oxygen sensors[84–90] as well as their biocompatibility[90–98]. Right now, several human protocols using EPR are ongoing in Dartmouth[81–83, 99, 100] and clinical studies have also been recently started in Brussels and in Emory. We will describe them later in this publication.

THE CONTRIBUTION OF HAL SWARTZ TO SCIENCE: A TOPIC-ORIENTED PERSPECTIVE ON HIS CAREER

It is not easy to 'categorize' Hal Swartz as this open-minded person contributed in many ways and in many fields of physiology and medicine. Still, we may identify at least four emerging themes that have been pursued continuously along his career since its

beginning: (1) radiation biology; (2) oxygen and oxidation; (3) measuring physiology *in vivo*; and (4) application of these measurements in clinical medicine. The common feature among all these different subjects has been the use of magnetic resonance techniques, especially EPR (Figure 4).

At the beginning of his career, he received advice to focus on scientific problems, and not on techniques. Hal Swartz is quite proud to say that he never followed this advice, and focused his career on a specific technique (i.e. EPR). '*To succeed, you need to have 'something' you can do better than anyone else*'. Hereafter, we present some of his major contributions in these areas, a subjective 'Best of' among a long list of more than 500 publications in high-quality peer-reviewed journals.

His contribution in radiation biology

Studying the effect of radiation of tissues has been a continuous effort from the early days to the today's research of Hal Swartz. When Hal started his research in the Walter Reed Army Institute of Research, his first EPR studies were on irradiated animals and the evidence for the presence of long-lived radicals induced in the tissues. In the second paper of his career that was published in 1965, Hal Swartz demonstrated the prolonged existence of radiation-induced unpaired electron species in the femurs of rats that were irradiated *in vivo*[101]. In the discussion of this paper, he already suggested '*the use of radiation-induced ESR signals as in vivo dosimeters in accidental radiation exposures*'. Later, he carried out a systematic study to look to the sensitivity of tissues to provide EPR signals after irradiation[102]. He demonstrated the high sensitivity of teeth at low dose of irradiation (Figure 5). As this biological material was more easily accessible than bones, he concluded his paper by saying: '*Electron spin resonance measurements of radiation-induced resonances in teeth appear to offer a potential in vivo dosimetry system for accidental radiations*'[102]. These works stimulated over time a considerable effort over the world to better characterize the nature of these free radicals[103–112], and to better define how these tools can be used in epidemiology or in the management of accidental irradiation[113–118]. One of the limitations he mentioned in the discussion of this key paper[102], the '*obvious problem in sample procurement*', was alleviated 40 years later thanks to the instrumental developments carried out in his lab to build the first clinical EPR facilities[80, 81, 119–126].

The interest of Hal in radiation biology has not been limited to retrospective dosimetry. The modulation of the radiation sensitivity has been also a continuous and very productive area of his research. As already mentioned, his early works were done on chemicals that could protect against radiation damages[4, 5, 127]. The structure-relationships studies that Hal carried out at that time on mercaptoethylamines homologues are still a reference for today's handbooks, as this class of compounds is almost the only one identified so far for this biological effect. His interest was later focused on the possible increase in radiation sensitivity of tumors through an oxygen effect. It is indeed known that oxygen plays a key role in the radiation damages in cells. The work of Hal's group first focused on the characterization of the timing of reoxygenation after irradiation[62–64, 128–131]. Again, this initial work stimulated other EPR groups to identify key determinants of this reoxygenation[132–135], and has been a driving force to transfer EPR oximetry in clinical practice. More recently, the group of Hal[131, 136–144], in parallel to other EPR groups[88, 135, 145–172], focused his interest on the pharmacological modulations of the tumor pO_2 to render tumors more sensitive to irradiation. The contribution of Hal Swartz in radiation biology

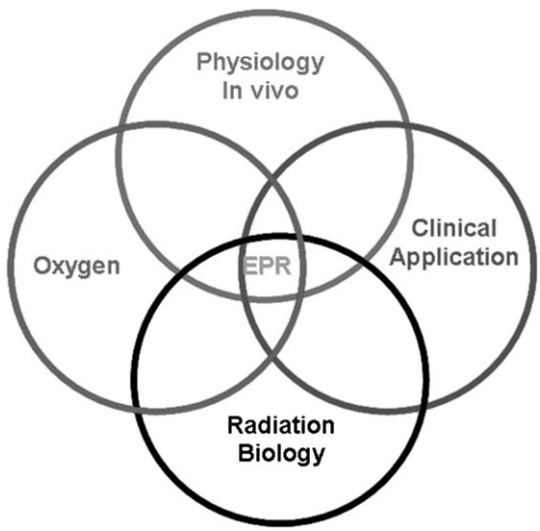

Figure 4. The four major fields of interest during the scientific career of Hal Swartz, with their overlaps and the common feature of using EPR as a tool to explore these topics.

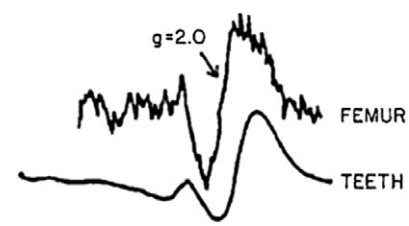

Figure 5. Demonstration of the presence of EPR signals in bones and teeth of rats irradiated *in vivo*.

has not been only experiment in tissues or animals. Important publications and statements have been published by Hal during his career on the radiation hazards, specially in relationship with radiological examinations[173–176].

His contribution on the study of oxygen and oxidation

The interest for oxygen and oxidation has been continuous since the early steps of Hal Swartz in research up to today's work. This was actually the center part of his PhD thesis entitled 'Effect of oxygen on freezing damage in *E. coli*'[177] and the associated papers[178–181]. The central issue of his research has been to establish the critical relationship between the local oxygen concentration and its physiological role or potential toxicity. Convinced of the importance of this issue, and frustrated by the available methods able to provide accurate and sensitive measurements of oxygen, has been a driving force for him to develop and improve the methods for measuring oxygenation in cells and tissues, and to apply them to solve important biological and physiological problems. Oxygen being paramagnetic, but not directly detectable by EPR in biological media at physiological temperature, several generations of researchers in his laboratory worked on the characterization of oxygen sensors. Most EPR oximetry methods rely on the paramagnetic properties of molecular oxygen that acts as an efficient relaxer for other paramagnetic species. The most common method is to use the line broadening of the hyperfine line (related to T2). After dozens of years of research, does it succeed in finding the ultimate oxygen sensor? Actually, success has come from many candidates, all of them being adapted for specific purposes[182]. The first sensors that have been used were the nitroxide radicals. Using these soluble chemicals, extensive work has been performed by his team to measure oxygen in the intracellular compartment and within subcellular structures[19, 21, 183–188]. Later, evidence was found that the plasma membrane cholesterol was the likely barrier to intracellular oxygen responsible for this gradient[189]. From his initial interest for nitroxides as oxygen reporters, came also the problem of the rapid metabolism of these compounds and the loss of paramagnetism. His group made an in-depth study on the key factors that were responsible for the metabolism of the nitroxides in diamagnetic hydroxylamines: structure–activity relationships, identification of the sites of metabolism *in vitro*[24, 183, 190–200]) and *in vivo*.[43] His group found out that one major factor responsible for the metabolism was the redox status of the cells. He immediately understood the value of turning the problem of metabolism into virtues, and developed the concept of functional contrast agents, that are sensitive to the oxygenation and to the redox status (Figure 6)[20, 22, 23, 25].

At this time, this suggestion was not directly applicable for *in vivo* EPR as the technique was at its very early days. The idea was to use nitroxides as MRI contrast agents. The seminal ideas of using these compounds as redox-sensitive contrast agents are still actively developed by other groups in EPR imaging[159, 201–206], MRI[43, 203, 204, 207–210], and Overhauser MRI[203, 211, 212]. Very importantly, these works have contributed to the idea of developing 'smart agents' that are activated only in the presence of a key factor present inside a tissue. Several generations of chemists are still actively working in this field of molecular imaging.

The recognition of the potential value of oxygen-sensitive particulate paramagnetic materials[74–77] has had a very strong impact on the development of EPR oximetry[147]. These materials have several characteristics that are not shared by soluble free radicals. They have a much larger sensitivity (up to 1000 times that of soluble materials) to oxygen, in terms of the magnitude of the change in line width per unit of oxygen (Figure 7). These materials also tend to be unreactive; they remain stable despite the presence of oxidation, large changes in pH and presence of other paramagnetic materials. A big advantage of these materials is their capability of providing repeated, sensitive and accurate measurements of pO_2 at the same site. Early in the 90s, his group started to discover and characterize the unique properties of several particulate oxygen sensors[74] such as lithium phthalocyanine[75], coals such as fusinite[76] and gloxy[77], sugar and wood chars[213, 214]. This early work stimulated considerable amount of work in other EPR centers to identify new sensors to oxygen or other paramagnetic gases[87, 89, 215–217]. Among the oxygen sensors that have been identified in Dartmouth, India ink has been probably the most unexpected but the most important discovery for motivating the transfer of EPR oximetry into the clinic[79], as India ink is used in humans for 'cosmetic' purposes or as markers before surgery. Again,

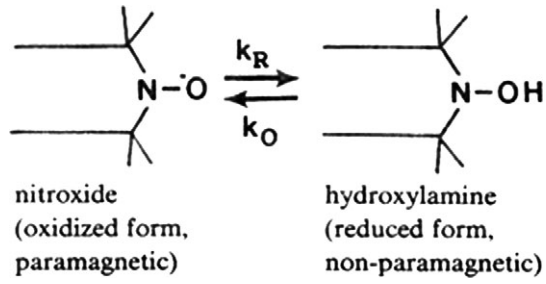

Figure 6. Redox-dependent metabolism of nitroxides as a basic concept of smart contrast agents.

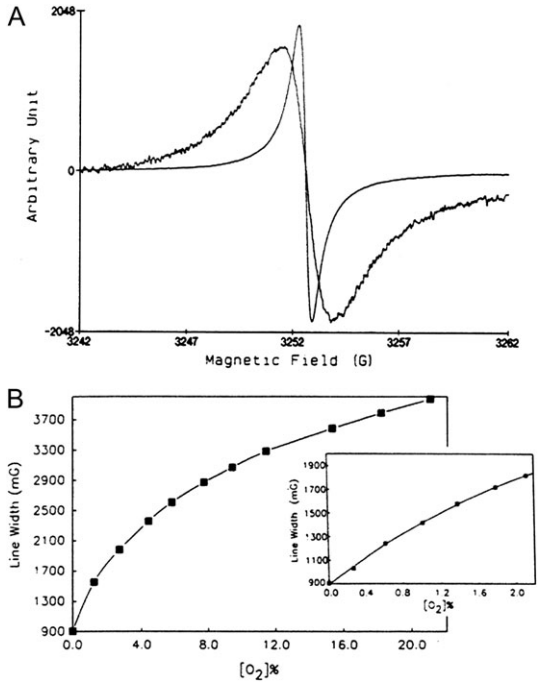

Figure 7. EPR signal from fusinite particles. (**A**) Change of the EPR linewidth as a function of the oxygen environment. (**B**) Relation of the linewidth of fusinite to the concentration of oxygen; inset shows relationship at the lower concentrations of oxygen that are of most interest biologically.

this work stimulated intense research for identifying better carbon blacks candidates (the active paramagnetic material contained in the inks)[89] and for improving the characteristics of biocompatibility of the particulate oxygen sensors[90–94, 96, 97, 218, 219].

The particulate oxygen sensitive materials have been particularly useful for measuring the oxygenation level in several tissues under physiological or pathological conditions, and during therapies. A major interest has been focused on tumors[42, 62–64, 130, 131, 140, 141, 143, 220, 221] because tumor hypoxia has been known for a long time to be an important physiological parameter in tumor growth and response to therapy. We already mentioned the work done on the reoxygenation of tumors after irradiation. Other works on tumors involve the evolution of oxygen during photodynamic therapy[139, 222, 223], or after pharmacological challenges[140–143]. Another important topic has been focused on the evolution of the brain oxygenation during ischemia and models of stroke[51, 224–227]. The oximetry studies have not been limited to the previous topics, and other investigations have been carried out on heart[48–50, 52, 228, 229]), kidneys[67, 72], liver[230, 231] and skin[232, 233]. Again, these developments in oximetry have stimulated a considerable body of work in other EPR centers over the world to measure oxygen in different tissues such as brain[234–239], heart[240–250], muscles[251–253] and tumors[88, 135, 145–162, 170, 254–270].

Finally, it should be emphasized that it was not an easy task to impose EPR oximetry as an emerging technique to measure oxygen in tissues. Any new technique is often criticized, especially when it seems that it is superior to previous standard methods in terms of sensitivity. Hal Swartz was very clever at initiating comparisons of EPR oximetry with other techniques such as oxygen electrodes[271, 272], nitroimidazoles[222], quenching of fluorescence[273], near-Infra Red[274], BOLD MRI[136] and dynamic contrast-enhanced MRI[62]. A very important issue that came from these studies is the nice complementarity of the techniques[275]. Rather than trying to identify the best tool, it is better to understand complex physiological processes and dissect their mechanisms by taking advantage of the specificity of each technique.

His contribution in measuring physiology *in vivo*

Since his first research studies, Hal Swartz tried to use EPR to solve important biological problems related to radiation biology or the importance of oxygen in cells. More importantly, he early understood the unique value of transposing the technology to study not only *biological problems* but *biological systems*. In comparison to NMR, they are considerable technical challenges that make *in vivo* EPR difficult[276]. The usual frequencies used for EPR in physics and chemistry are too high for use in tissues, because of non resonant absorption by water. It is worthwhile to remember briefly some highlights on the development of *in vivo* EPR[277]. The first studies in EPR at the usual frequency (9 GHz) on wet tissues or suspensions of cells were made possible by the development of flat cell and tissue cells. Still, these holders were not adapted for *in vivo* studies. The pioneering experiment by Feldman *et al.*[278] is considered as the first *in vivo* EPR study. They implanted a resonator in the liver of a rat receiving an injection of Tempol. This experiment suffered from a major problem: the overheating of the tissues by the 9 GHz irradiation. To move really in a more physiological situation, the crucial steps were the construction of low frequency spectrometers as suggested by Hutchison[279] and the development of resonators designed for *in vivo* experiments. The first prototype L-Band (1 GHz) spectrometer was constructed in the first EPR center in Milwaukee, and the development of the loop-gap resonator by Froncisz and Hyde[8] was a major breaktrough for *in vivo* EPR, followed by the first EPR oximetry study[280]. These early developments stimulated other

laboratories to pursue EPR spectroscopy *in vivo*. In the mid-80s, Berliner and colleagues evaluated the feasibility of imaging biological systems by EPR at this low frequency[281, 282], while Zweier and Kuppusamy[246] reported the observation of nitroxides in the intact beating heart, and Halpern developed very low field *in vivo* EPR imaging[283].

What about the activities of Hal Swartz during this period of time? His group focused on the use loop-gap resonators to develop surface coil resonators[284], a design that is still used 30 years later in the first EPR clinical applications. We may say that the driving force of his developments of *in vivo* EPR has been to put the biological problems as the central question. Early works focused on problem of diffusion in tissues[28], pharmacokinetics of drugs[285], spatial resolution[29, 30], metabolism[286] and of course oximetry[32, 33, 287]. Then, in the 90s, started the fantastic developments in EPR oximetry using the solid paramagnetic oxygen sensors and their application in physiology and medicine (see the previous section for the description). Besides oximetry, he realized also the power of the technique to measure *in vivo* other important physiological and pathophysiological parameters. As illustrative examples, his group developed in the 90s new applications on the metabolism of metallic compounds[44, 65, 66, 69, 70], the detection of free radicals by *in vivo* spin trapping[54, 68, 71], the use spin labeling technique to monitor systems of drug release[55, 57–59], and the first applications of pH measurement using *in vivo* EPR[56, 57].

His willingness to apply EPR in the clinic

'Applying EPR from cells to mice to men', this shortcut summarizes a leitmotiv and a fantastic achievement of his career. In his first paper published in 1965 on the detection of stable free radicals in irradiated bones[101], he already suggested an application of EPR in humans. In 1973, in his paper entitled 'A survey of present and potential clinical applications of Electron Spin Resonance' that was published in the Annals of the New York Academy of Sciences[78], he tried to predict the potential clinical applications of EPR. At that time, *in vivo* EPR was not yet developed, and he focused his paper on possible changes occurring in blood during carcinogenesis and on EPR changes as markers of viability. If these two areas were eventually not the most successful, he recognized that '*if an esr spectrometer that could be utilized in vivo without removing the specimen from the animal could be successfully developed, some of the current limitations on clinical applications of esr would be removed*'. We already focused on the key developments that were carried out in the 80s to render *in vivo* EPR possible. Early in the 90s, he published a paper 'In vivo EPR: prospects for the 90's'[288] that was a state-of-the art of the field. It was irresistible for him to predict the future of *in vivo* EPR. He made the key assessment that *the most important factor in the use of in vivo EPR techniques will be whether they provide better and/or different information than can be obtained by other techniques*. In this paper[288], he already identified two major areas meeting these criteria: *in vivo* EPR oximetry and retrospective dosimetry.

The principal technical challenges for adapting *in vivo* EPR in the clinical setting were the adaptation of the instrument for accommodating human subjects. This is still a major field of research for the moment in his EPR center in Dartmouth. During the last years, his group developed unique large EPR instruments[80, 81, 99, 289] with the capability to position the patient comfortably and accurately within the magnet.

Another crucial aspect was to assure the safety of materials administered for *in vivo* EPR. With the development of particulate oximetric probes[74–77, 83, 290], Hal Swartz was in a position to claim the unique capability of EPR to make repeated measurements of local oxygen concentration with a sensitivity that is larger than using any other technique. One of the key advances was the identification of India inks as containing stable free radicals that are sensitive to oxygen. This led to the first human experiment made on an arm bearing a tattoo[79](Figure 8).

This was definitely not the best oximetry probe that was identified so far. But, this compound had

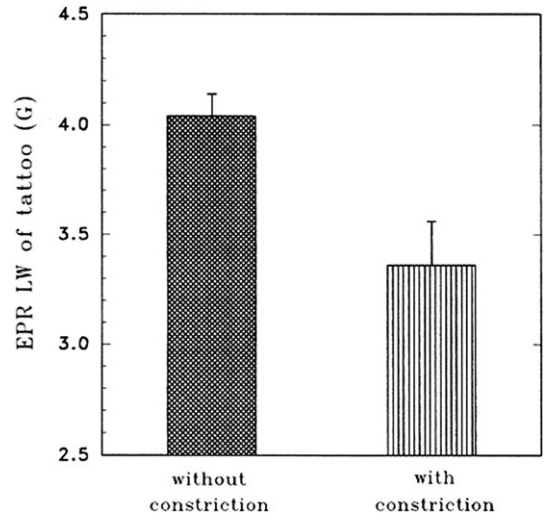

Figure 8. First *in vivo* human EPR oximetry study from a tattoo. Effect of the oxygen environment on the EPR linewidth: the spectra were obtained before and after the constriction of the blood flow by means of a rubber tourniquet around the arm[79].

the unique advantage to be used in humans for decoration as tattoos since millenia. Moreover, it is commonly accepted as a standard procedure in the clinic for permanent marking for radiation therapy and endoscopic treatments. Therefore, the door was open for a transfer of EPR oximetry into the clinic[83, 291], by-passing the need for a long process of making acceptable a drug by health agencies. Unfortunately, the EPR characteristics of these first inks were not optimal (low density of spins, multi-component signal). This stimulated a considerable amount of research that was carried out by us and Hal Swartz's group to identify new sensors among commercially available materials. Even if some useful compounds were identified, the EPR properties varied from one batch to another within the same trademark. Finally, it turns out that the best way to go was to isolate an active component of ink (carbon black[89]) and to prepare a synthetic ink using dispersing agents commonly used in pharmaceutical suspensions for injections[94]. The other strategy that was followed was to prepare oxygen materials in permeable biocompatible implants[91–93, 96, 97, 219, 292, 293] that could be used as retrievable inserts or part of catheter resonators that were also developed in Hal Swartz's laboratory.

Several clinical protocols using EPR are ongoing in his laboratory for the moment. The first one is focused on the measurement of oxygen in tissues. The initial phase includes human volunteers that have been injected with a synthetic ink[94] in their foot to measure the pO_2 in the subcutaneous tissue. It is worthwhile to mention that Hal Swartz has been one of the first volunteers for these experiments (Figure 9).

The approach of these studies is to enroll patients with peripheral vascular diseases (i.e. diabetic patients) for whom the capability of repeating measurements of pO_2 in their limbs would be of high clinical value. The second set of patients who will be selected for a clinical evaluation of the technique will enroll cancer patients. To date, measurements have been performed in several volunteer patients with tumors in which India ink has been injected (Figure 10)[81–83, 289] and indicate that it is likely than EPR oximetry can be used successfully in the clinical setting to measure tumor pO_2 in humans. In the next phase, they will enroll a series of patients who will receive radiation therapy. These EPR clinical protocols have now been enlarged to two other centers, in Brussels (B. Gallez) and in Emory (A. Arif). In pre-clinical studies, it was one of the successes of *in vivo* EPR to show the value of predicting the time of reoxygenation[62–64, 128–135]. Clearly, the possibility to repeat pO_2 measurements over the time in the time course of a radiotherapy treatment could be a great advantage in order to identify the period of the maximal radiation sensitivity of the treated tumors.

In addition to oximetry, another field of clinical application is actively pursued by Hal's group: the application of EPR for retrospective dosimetry. About 50 years after his first measurements in the Walter Reed Army Institute of Research on irradiated biological samples, Hal found also a unique opportunity for a transfer of this basic research into a clinical situation. Here, there is no need for an administration of paramagnetic compounds as EPR detects the presence of radiation-induced stable free radicals in teeth as a dosimetry marker[102]. Tremendous instrumental developments have been carried out in his laboratory to achieve this goal to adapt the settings used on rodents for this purpose[99, 294] to develop a unique human EPR dosimeter[120–123, 295]. The results obtained so far are quite spectacular, and are likely the most accessible and

Figure 9. Hal Swartz as volunteer of his first clinical EPR study. Note that, even during his oxygen challenge protocol, he tried not to waste time.

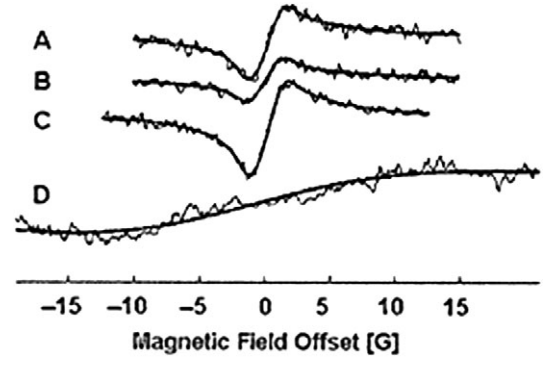

Figure 10. Clinical EPR study. Response of tumor pO_2 to breathing 100% oxygen in a volunteer with a subcutaneous lymphoma.

easy tool to sort large populations in case of nuclear emergency due to accidents or terrorist attacks[99, 120, 121, 296].

Importantly, Hal Swartz started the first clinical EPR experiments in areas where he is an expert and where he had a chance to succeed and prove the uniquiness of the information given by the technique. Very interestingly, the technique may even offer much more applications where EPR possess unique capabilities: spin trapping of important free radicals (such as nitric oxide), spin labeling to measure microviscosity and macromolecular motion, metals, redox status, etc.[295]. If successful, the developments made by Hal Swartz will totally change the way EPR spectroscopy and imaging are perceived in the medicine community. And many other EPR applications will become feasible in the clinic!

HAL SWARTZ AS A MENTOR

As already mentioned, Hal Swartz established three NIH-funded EPR centers along his career. These centers offer a great opportunity for scientists to find at the same place unique instruments and unique expertise. These centers became outstanding catalysts for researchers. Actually, this becomes later also the seminal idea to create the international EPR society. These places were visited by numerous scientists for short or long periods of time. Hal Swartz directed and trained many scientists. His present center is still very active and productive, with extensive funded projects, and has several brilliant researchers. Maybe, one of the most remarkable achievements of his career has been the dissemination of his ideas through the creation of other research centers directed by his formers post-docs, who can be considered as his academic sons and daughters. Through extensive collaborations and a continuous instrumental support, he created a worldwide network of people who are still clearly influenced by the research they did together with him. The list hereafter is more illustrative than exhaustive. In USA, A. Smirnov (Raleigh, NC), J.F. Glockner (Rochester, MN), C. Mailer (Chicago, IL), M.J. Nilges (Urbana, IL), K.J. Liu and G. Timmins (Albuquerque, NM), I. Salikhov (Columbus, OH), W.S. Enochs (Philadelphia, PA), J.J. Jiang (NIH, NC), P.L. Gutierrez (Baltimore, MA), W.E. Antholine (Milwaukee, WI). In Japan, H. Hirata (Sapporo), T. Nakashima (Kyoto), F. Goda, A. Irwasaka, S. Tiae, and M. Miyake (Kagawa), T. Suzuki-Nishimura (Tokyo). In Europe, M. Sentjurc and F. Demsar (Lublijana, Slovenia), K. Mäder (Halle, Germany), P.E. James (Cardiff, UK), G. Bacic (Belgrade, Yougoslavia), A. Tomasi and A. Ianonne (Modena, Italy), T. Sarna, W. Froncisz, J.W. Dobrucki (Krakow, Poland), P. Gast (Leiden, Netherlands), B. Gallez (Brussels, Belgium). Most of these scientists are pursuing their own works and writing some important pages of the EPR story or related matters, still with a large influence from their previous mentor.

HAL SWARTZ AS A FOUNDER OF SCIENTIFIC SOCIETIES AND ORGANIZER OF SCIENTIFIC MEETINGS

A fascinating feature of Hal Swartz is his ability to organize conference, societies where people can meet and exchange on rapidly evolving domains. Historically, one of the most important conferences he organized was the 'Gordon Conference on Magnetic Resonance in Medicine and Biology' in June 1974 (Figure 11). At that time, the aim of the conference was to try to sort out areas of controversy in use of magnetic resonance methods in the study of cancer. On the EPR side, people were looking at the various theories and claims relating free radicals to cancer[297–302]. On the NMR side, there were controversies regarding whether NMR relaxation times gave a specific diagnostic indication of the presence of cancer[303, 304]. The idea of Hal Swartz at that time was to bring together principal individuals on both sides of both controversies, to stimulate discussions to resolve the controversies or to guide the experiments to be done to resolve them. At that time, he also invited Paul Lauterbur who had just published about a strange method called 'zeugmatography' in the journal Nature, where he actually described the principle of MRI[305]. For this discovery, P. Lauterbur received the Nobel Prize in 2003. This Gordon Conference organized by Hal was followed by a period of strong interactions between people involved in the development and application of magnetic resonance in biology.

The leaders in the field decided to create a scientific society. At that time, the name 'Society of Magnetic Resonance in Medicine' (avoiding the word 'nuclear')

Figure 11. Participants to the Gordon Conference on Magnetic Resonance in Medicine and Biology, June 1974. On the bottom row, you may recognize R. Damadian, P. Lauterbur and H.M. Swartz next to each other.

Figure 12. Hal Swartz receiving from R.P. Mason the special gold medal of the International EPR Society as founder president (2005).

was chosen to make sure that EPR was included. In the first board of directors of the society, Hal Swartz was the only person from the EPR side. He actually was member of the board trustees of this society from 1982 to 1990, and its secretary from 1985 to 1990. His presence at that time in this emerging field has been essential to allow the communications and publications of EPR studies in this society essentially oriented to NMR questions.

Hal Swartz has been also the first organizer of international meetings on 'In vivo EPR spectroscopy and Imaging'. The first meeting was organized in Urbana in 1986, followed by a long series of meetings. Later, he organized again this meeting in 1993, 1998, 2001, 2004 and 2013 in Dartmouth. All researchers active in this field acknowledge his fantastic organizing capability and the way he conducted these meetings, by strong interactions in an intimate, intense and relaxing atmosphere. This definitely contributed to strong collaborations among different researchers over the world and to rapid progresses by a rapid dissemination of the information.

Hal Swartz also organized scientific meetings less technologically oriented, but more oriented on specific questions. Hence, he organized several meetings of the International Society on Oxygen Transport to Tissue (ISOTT) and EPR-BIODOSE (International Conference on Biodosimetry). This is likely because Hal Swartz is quite convinced that solving a biomedical problem is more likely to occur by a set of complementary techniques rather than by a single technique or a competition between techniques.

Last but not least, Hal Swartz has been the founder of the International EPR (ESR) Society. We find here again his desire to put people together through a worldwide connection. The scale is definitely larger than the previous audience cited. '*Connecting scientists to make science better*' seems to have been the device of Hal Swartz along his career.

INTERNATIONAL RECOGNITION

The excellence of his research and its impact on the field has been so high that Hal received many outstanding awards during his career. These awards have been provided not only for his fantastic contribution to the Science, but also for the considerable efforts to organize scientific societies in order to facilitate the environment and the connection between scientists. To cite only the most important ones, he received in 1993 the Silver Medal from the Society for Magnetic Resonance in Medicine. In 1994, he received the Silver Medal (Biomedicine) from the International EPR Society. In 1997, he was distinguished as a Fellow of International Society for Magnetic Resonance in Medicine. The year 2005 was particularly prolific in outstanding awards, as he was distinguished as Fellow of the International EPR Society, and he received a special gold medal as founder of the International EPR Society (Figure 12).

Finally, on September 28 2005, he received the prestigious Zavoisky award in Kazan, the capital city of the Republic of Tatarstan. It was there that academician E.K. Zavoisky discovered EPR in 1944. The ceremony marked his outstanding contribution to the development of *in vivo* EPR and EPR oximetry for clinical applications.

CONCLUSION

We started this article with reference to painting and to impressionists. I wish to conclude with another famous painting of a Belgian surrealist, René Magritte. 'This is not a pipe'. Of course, when you see a painting of a pipe, you know that this is not a pipe. A true pipe, you can touch it, you can smell it. It is just a 'depiction' of a pipe. Accordingly, we may say about this portray, 'This is not Hal Swartz'. This brilliant scientist and gentleman is much more than his portrait!

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