The Founding of ISOTT: The Shamattawa of Engineering Science and Medical Science

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Abstract This paper expands upon past writings and reflects the truism stated by Confucius, "Study the past if you would define the future." The founding of ISOTT was based upon the blending of Medical and Engineering sciences. Beginning with Carl Scheele's discovery of oxygen, the medical sciences advanced the knowledge of its importance to physiological phenomena. Meanwhile, engineering science was evolving as a mathematical discipline used to define systems quantitatively from basic principles. In particular, Adolf Fick's employment of a gradient led to the formalization of transport phenomena. These two rivers of knowledge were blended to found ISOTT at Clemson/Charleston in 1973. The future will be determined.

1 History

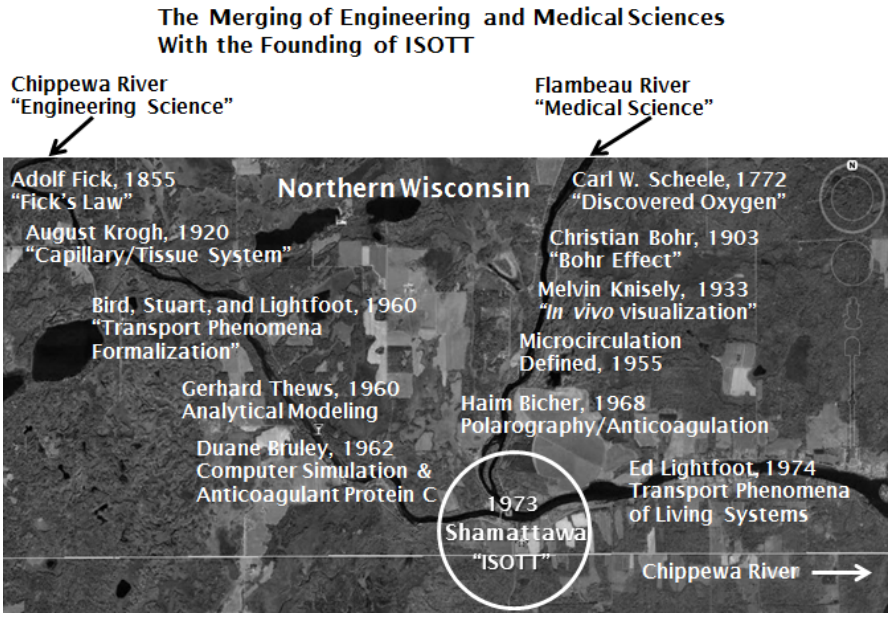

Fig. 1 The formal merging of engineering science and medical science in oxygen transport to tissue

The wise man Confucius once said, "Study the past if you would define the future." In consideration of this insight, I have thought back to my early life in Northern Wisconsin where I have spent a great part of my life hunting and fishing. I think about the Chippewa River and the Flambeau River (Figure 1) and how they meet at what is called the "Shamattawa" (the confluence of two rivers). Similarly, I view the founding of ISOTT as the merging of engineering science and medical science. While there are many important players on both sides, we can only highlight a few due to space limitations. A historical review of this development starts with the discovery of oxygen by Scheele in 1777[1] (Flambeau River), while on the engineering science side, the concept of transport phenomena started with Adolf Fick in 1855[2] (Chippewa River). Following the discovery of oxygen, scientists such as Christian Bohr[3] and Melvin Knisely[4] evolved the medical sciences through their studies and observations. On the engineering science side, with the concept of Fick's Law, August Krogh applied Fick's Law involving the oxygen gradient in tissue.[5] At a later date, Bird, Stewart, and Lightfoot formalized the discipline of transport phenomena in inanimate objects.[6] Gerhard Thews expanded on Krogh's conceptualization of a tissue cylinder,[7] which was further refined by Duane F. Bruley using complex computer simulations to represent the Krogh capillary cylinder.[8] Following this, Haim Bicher used microelectrodes and polarography to corroborate with the mathematical simulations to demonstrate that gradients exist in the tissue, focused on the grey matter of brain.[9] In these early days, the microcirculation was formally defined (1955). ISOTT was then established at the Clemson/Charleston founding meeting in 1973,[10,11] which then followed with the application of transport phenomena to living systems by Ed Lightfoot in 1974.[12] ISOTT being built on this merging over the years has been firmly established with an innovative approach to the future.

This paper is an enhancement and extension of the presentations and papers prepared for the 1997, 2006, and 2010 *International Society on Oxygen Transport to Tissue* meetings.[13,14,15] Similar to most successful research projects it was a serendipitous process. Throughout the early years there have been many meetings related to oxygen transport in tissue and several societies that promoted sessions on the subject prior to the founding of a formal society.

Colleagues, on occasion, have told me that there were discussions regarding the possible establishment of a society on oxygen transport prior to 1973. If that is true I was never a part of any of the discussions nor was I even contacted by a colleague to be part of such an effort. Also, I have been asked whether or not Dr. Knisely approached me to create a symposium in his honor or to form a society. Just for clarification, I never had any discussions related to the development of a symposium or a society with Dr. Knisely prior to gaining permission from Clemson to host a meeting at Clemson University in 1971.

My formal education was in traditional chemical, mechanical, and nuclear engineering. In the fall of 1962 I accepted a position as Assistant Professor of Chemical Engineering and Head Varsity Tennis coach at Clemson University in Clemson, South Carolina, USA. That fall a colleague, Dr. William Barlage, and I were discussing possible new research areas; thus, we decided to take a five

hundred mile round trip to the Medical College of South Carolina in Charleston, SC to see if there were problems involving "living systems" that we could apply our engineering skills to. Being traditional engineers neither of us had a formal education in the biological or life sciences and had studied only non-living systems. To clarify, even though traditional engineers can make significant contributions to the engineering of living systems a new breed has evolved, the Bioengineer, which represents the fifth traditional discipline of engineering.[16] A definition that I have frequently used for bioengineering is as follows: "Bioengineering is the application of engineering principles and fundamentals to engineering problems that *require* basic understanding of the biological and/or life sciences." This definition states that modern Bioengineers must have a formal education that includes the biological and/or life sciences thus giving them insight into processes involved in living systems that would not be obvious to traditional engineers. This concept has a *foundation* in the principles upon which ISOTT was established.

On the second day of our visit to the Medical College and after several meetings, without success, we were standing outside of the Anatomy Department when Dr. Melvin H. Knisely (Head of the Department) appeared and introduced himself. After a brief discussion he invited us to lunch where he stated his interest in mathematical modeling and computer simulation of oxygen transport in the grey matter of brain. He was concerned about the viability of neurons under different pathological conditions and he thought that computer predication could be valuable.

This problem was of interest to me since I had recently completed my Ph.D. dissertation that included experimental and theoretical work on the thermal dynamics of a wetted-wall-column.[17] My theoretical model consisted of a computer simulation of a coupled set of partial differential equations describing simultaneous heat and mass transfer in cylindrical coordinates. The equations contained terms for convection and conduction in two space dimensions and time and were solved using finite difference techniques *via* Fortran programming. We developed the *Direct Substitution Method* for solving PDE's. This research fit perfectly with the description of the Krogh Capillary Tissue model and the problems associated with the solution of representative models that scientists and engineers around the world were then exploring to quantify the microcirculation. After a year of study to learn the necessary physiology and anatomy and the translation of two German articles, one by Opitz and Schneider[18] and the other by Thews[7] (help in translation was provided by Isebel Lockard and Elsie Tabor in Dr. Knisely's Laboratory) I derived a mathematical model, from basic principles (the Bruley Model), that was solved by various graduate students on digital, analog and hybrid computers, for different anatomical and physiological conditions.[8,19] This research represented the first computer simulations of the microcirculation, and a major step forward in quantitative analysis because computer simulation allowed investigation of the dynamic and non-linear characteristics of the system in two and three space dimensions, and for multi-components.

These studies started in 1962 and we worked together until Dr Knisely's death in 1975. During that period we published around 30 papers together regarding theoretical and experimental investigations of oxygen transport to tissue.

In 1968 Dr. Haim I. Bicher was recruited to our team because of his knowledge of blood agglutination and his expertise in the construction and use of oxygen micro electrodes. His contribution to our research effort allowed us to work back and forth between theory and experiment thus giving us the best possible research environment. We presented our work primarily at the European Microcirculation meetings and published in a variety of journals. It was then that we started to examine anti-adhesive drugs in an attempt to prevent clotting and to reverse the consequences of blood agglutination.[9] This initial work has led to my current studies of Protein C, a blood factor that might be the ultimate anticoagulant/antithrombotic/anti-inflammatory/anti-apoptotic for Protein C deficient patients, because there are little or no known side effects with the zymogen such as bleeding complications.[20]

In 1971 our team attended a workshop on "oxygen supply" at The Max-Planck Institute in Dortmund, Germany, organized by Manfred Kessler and Dietrich Lubbers.[21] It was then that I decided to inquire about sponsoring a symposium at Clemson University to highlight our team work with Dr. Knisely's group at The Medical School of South Carolina. Immediately after I returned to the United States I asked Dr. Edwards, the President of Clemson University, for permission to host an oxygen transport to tissue symposium at Clemson University and with it honor Dr. Melvin H. Knisely for his many contributions to the field of microcirculation. In particular I wanted to honor him for his development of the quartz rod crystal illumination technique that allowed him to visualize the sticking together of blood components, *in vivo*.[4] Dr. Knisely observed this phenomena in cases of malaria and over one hundred other disease states. He hypothesized that this condition leads to oxygen deprivation which could cause sickness and death. Permission was granted so I called Dr. Knisely's wife, Verona, to find out what she thought about it. After a short time Verona called back and said it was a good idea but she thought it would be better to have the symposium at The Medical College of South Carolina. With further discussion we decided to have a symposium at both campuses, with bus transportation in between. Both Dr. Edwards, President at Clemson University and Dr. McCord, President of The Medical School of South Carolina agreed to help fund the symposium.

When Dr. Bicher returned from an extended trip to Israel, I asked him if he would like to participate in setting up the symposium. He was anxious to do so and he then took responsibility for further arrangements at the Medical School while I handled all arrangements at Clemson University and the combined meeting. Together we obtained additional support from other companies and agencies to fund the meeting.

The intended purpose of the symposium was to promote interdisciplinary and cross-disciplinary research involving theoretical and experimental investigations for oxygen transport in tissue. It was to bring together life scientists and engineers

in a single session format to examine the many complex phenomena of normal tissue growth and maintenance, and tissue survival and repair under pathological conditions. This has remained the mission for ISOTT since its birth and is probably the precursor to what is defined as *Tissue Engineering* today.

After an intensive period of planning and preparation an initial meeting announcement was sent out to sample community interest. The results demonstrated enthusiasm far beyond projections and triggered Drs. Bruley and Bicher to consider the meeting as a launching pad for a very focused international society regarding oxygen transport to tissue. We presented our idea to several other investigators and then we decided that a formal society would be in the best interest of groups around the world to achieve research goals related to oxygen transport in tissue and that the Clemson/Charleston meeting would be an appropriate forum to formalize and begin an international society. We then decided on the name *International Society on Oxygen Transport to Tissue*, designed a society logo, assigned a mission, developed a charter, sketched the by-laws, contracted with Plenum Publishers to publish the meeting proceedings, and selected members to comprise an International Committee for the Clemson/Charleston meeting. The membership consisted of the following scientists and engineers:

Dr. Melvin H. Knisely, Charleston, USA
Dr. Haim I. Bicher, Charleston, USA
Dr. Ian A. Silver, Bristol, England
Dr. Britton Chance, Philadelphia, USA
Dr. Lars-Erik Gelin, Goteborg, Sweden
Dr. Manfred Kessler, Dortmund, Germany
Dr. William J. Whalen, Cleveland, USA
Dr. Dietrich W. Lubbers, Germany
Dr. Duane F. Bruley, Clemson, USA
Dr. Gerhard Thews, Mainz, West Germany
Dr. Herbert J. Berman, Boston, USA
Dr. Leland C. Clark, Jr., Cincinnati, USA
Dr. Jurgen Grote, Mainz, West Germany
Dr. Jose Strauss, Miami, USA
Dr. Daniel D. Reneau, Ruston, USA

Drs. Bruley and Bicher solicited Dr. Melvin H. Knisely to serve as an Honorary President of the Society for the initial symposium. At the 1973 Clemson/Charleston meeting, ISOTT was founded, and the following slate of officers was elected:

President-Elect- Dr. Gerhard Thews, Mainz, West Germany
Secretary- Dr. Haim I. Bicher, Charleston, U.S.A.
Treasurer- Dr. Ian A. Silver, Bristol, England

The first symposium of ISOTT surpassed all expectations and established a society that has continued to meet annually at various locations around the world. The registered participants numbered 267 and two volumes consisting of 133 papers were published by Plenum Press in their "Advances in Experimental Medicine and Biology" series[10,11] to represent the total Founding meeting (1973).

Society meetings have been held at the following locations under the leadership of the listed presidents:

1973	Clemson/Charleston, SC, USA	D.F. Bruley, H.I. Bicher (Founders, Co-Pres)
	Founding Meeting	M.H. Knisely (Honorary)
1974	Atlantic City, NJ, USA	D.F. Bruley, H.I. Bicher (Co-Presidents)
	Group Meeting	M.H. Knisely (Honorary)
1975	Mainz, Germany	G. Thews (First Elected President)
1976	Anaheim, CA, USA	B. Chance
1977	Cambridge, U.K.	I. A. Silver
1978	Atlantic City, NJ, USA	J. Strauss
1979	La Jolla, CA, USA	J. Strauss
1980	Budapest, Hungary	A. Kovach
1981	Detroit, MI, USA	H. Bicher
1982	Dortmund, Germany	D. Lübbers
1983	Ruston, LA, USA	D. F. Bruley
1984	Nijmegen, The Netherlands	F. Kreuzer
1985	Raleigh, NC, USA	I.S. Longmuir
1986	Cambridge, UK	I.A. Silver
1987	Sapporo, Japan	M. Mochizuki
		C. Honig (Honorary)
1988	Ottawa, Canada	K. Rakusan
1989	Gottingen, Germany	J. Piper
1990	Townsville, Australia	M. McCabe
1991	Curacao, Dutch Antilles	W. Erdmann
1992	Mainz, Germany	P. Vaupel
1993	San Diego, CA, USA	P.D. Wagner
1994	Istanbul, Turkey	C. Ince & K. Akpir (Co-presidents)
1995	Pittsburgh, PA, USA	E. M. Nemoto
1996	Dundee, Scotland	D.K. Harrison
1997	Milwaukee, WI, USA	A.G. Hudetz (25th Anniversary)
1998	Budapest, Hungary	A. Eke
1999	Hanover, NH, USA	H. Swartz
2000	Nijmegen, The Netherlands	B. Oeseburg
2001	Philadelphia, USA	D.F. Wilson
2002	Manchester, UK	M.S. Thorniley
2003	Rochester, USA	P. Okunieff
2004	Bari, Italy	G. Cicco
2005	Brisbane, Australia	D. Maguire
2006	Louisville, USA	K. Kang
2007	Uppsala, Sweden	P. Liss
2008	Sapporo, Japan	E. Takahashi
		M. Tamura (Honorary)
2009	Cleveland, USA	J. LaManna
2010	Ascona, Switzerland	M. Wolf
2011	Georgetown, USA	W. Welch
2012	Bruges, Belgium	S. van Huffel

The 2013 meeting will be held in Hanover, New Hampshire, USA, where Dr. Harold Swartz will serve as president. Dr. Clare Elwell will serve as president in London, England for the 2014 meeting and Dr. Qingming Luo and Dr. Lin Li will serve as co-presidents in Wuhan, China for the 2015 meeting.

In 1983 at the Ruston, Louisiana meeting Dr. Bruley initiated the first Melvin H. Knisely Award to a promising young investigator. This award was then approved and established by the Executive Committee and general membership to express the spirit and willingness of Dr. Knisely to work with and contribute to the growth of beginning scientists and engineers addressing the problems of oxygen transport to tissue. Dr. Bruley was then elected as the Chairman of the "Melvin H. Knisely Award" selection committee and nominees have been reviewed each year with those selected being honored at the annual banquet.

The recipients, through the 2013 meeting in Hanover, NH are as follows:

1983 Antal G. Hudetz (Hungary)
1984 Andras Eke (Hungary)
1985 Nathan A. Bush (USA)
1986 Karlfried Groebe (Germany)
1987 Isumi Shibuya (Japan)
1988 Kyung A. Kang (Korea/USA)
1989 Sanjay Batra (Canada)
1990 Stephen J. Cringle (Australia)
1991 Paul Okunieff (USA)
1992 Hans Degens (The Netherlands)
1993 David A. Benaron (USA)
1994 Koen van Rossem (Belgium)
1995 Clare E Elwell (UK)
1996 Sergei A. Vinogradov (USA)
1997 Chris Cooper (UK)
1998 Martin Wolf (Switzerland)
1999 Huiping Wu (USA)
2000 Valentina Quaresima (Italy)
2001 Fahmeed Hyder (Bangladesh)
2002 Geoffrey De Visscher (Belgium)
2003 Mohammad Nadeem Khan (USA)
2004 Frederick Palm (Sweden)
2005 Nicholas Lintell (Australia)
2006 No Awardee Selected
2007 Ilias Tachtsidis (UK)
2008 Kazuto Masamoto (Japan)
2009 Rossana Occhipinti (USA)
2010 Sebatiano Cicco (Italy)
2011 Mei Zhang (USA)
2012 Takahiro Igarashi (Japan)
2013 Malou Friederich-Persson (Sweden)

In 1994 a second Award to support travel for a young investigator was approved by the Executive Committee. The recipients of the "Dietrich W. Lübbers Award" are as follows:

1994 Michael Dubina (Russia)
1995 Philip E. James (UK/USA)
1996 Resit Demir (Germany)
1997 Juan Carlos Chavez (USA)
1998 Nathan A. Davis (UK)
1999 Paolo Pichiule (USA)
2000 Ian Balcer (USA)
2001 Theresa M. Busch (USA)
2002 Lino K. Korah (USA)
2003 James J. Lee (USA)
2004 Richard Olson (Sweden)
2005 Charlotte Ives (UK)
2006 Bin Hong (China/USA)
2007 Helga Blockx (Belgium)
2008 Joke Vanderhaegen (Belgium)
2009 Matthew Bell (UK)
2010 Alexander Caicedo Dorado (Belgium)
2011 Malou Friedrich (Sweden)
2012 Maria Papademetriou (UK)
2013 Nannan Sun

The Britton Chance Award was established in 2003 in honor of Professor Chance's long-standing commitment, interest and contributions to many aspects of oxygen transport to tissue and to the society. The award is to recognize outstanding contributions to research by a young investigator to help support travel to the ISOTT meeting. The Britton Chance Awardees are as follows:

2004 Derek Brown (Switzerland)
2005 James Lee (USA)
2006 Hanzhu Jin (China/USA)
2007 Eric Mellon (USA)
2008 Jianting Wang (USA)
2009 Jessica Spires (USA)
2010 Ivo Trajkovic (Switzerland)
2011 Alexander Caicedo Dorado (Belgium)
2012 Felix Scholkmann (Switzerland)
2013 Tharindi Hapuarachchi (UK)

The Duane F. Bruley Awards were established and were first presented by ISOTT at the 2004 annual meeting in Bari, Italy. They were established to support travel funds for student researchers in all areas of oxygen transport to tissue. The Awards signify Dr. Bruley's interest in seeking young scientists and engineers to maintain the image and quality of research associated with the society. As a co-founder of ISOTT in 1973, Dr. Bruley emphasizes cross-disciplinary research among basic scientists, engineers, medical scientists, and clinicians. His pioneering work constructing mathematical models for oxygen and other anabolite/metabolite transport in the microcirculation, employing computer solutions, were the first to consider system non-linearities, time dependence, including multi-dimensional, multi-component, diffusion, convection, and reaction kinetics. It is hoped that receiving the Duane F. Bruley Award will inspire students to excel in their research and will assist in securing future leadership for ISOTT. The Duane F. Bruley Awardees are as follows:

2004
Helga Blocks (Belgium), Jennifer Caddick (UK), Charlotte Ives (UK), Nicholas Lintell (Australia), Leonardo Mottola (Italy), Samin Rezania (USA/Iran), Ilias Tachtsidis (UK), Liang Tang (USA/China), Iyichi Sonoro (Japan), Antonio Franco (Italy)

2005
Robert Bradley (UK), Harald Oey (Australia), Kathy Hsieh (Australia), Jan Shah (Australia)

2006
Ben Gooch (UK), Ulf Jensen (Germany), Smruta Koppaka (USA), Daya Singh (UK), Martin Tisdall (UK), Bin Wong (USA), and Kui Xu (USA)

2007
Dominique De Smet (Belgium), Thomas Ingram (UK), Nicola Lai (USA), Andrew Pinder (UK), Joke Vanderhaegen (Belgium)

2008
Sebastiano Chicco (Italy)

2009
Lei Gao (UK), Jianting Wang (USA), Obinna Ndubuizu (USA), Joke Vanderhaegen (Belgium)

2010
Zareen Bashir (UK), Tracy Moroz (UK), Mark Muthalib (Australia), Catalina Meßmer (USA), Takashi Eriguchi (Japan), Yoshihiro Murata (Japan), Jack Honeysett (UK), Martin Biallas (Switzerland)

2011
Catherine Hesford (UK), Luke S. Holdsworth (UK), Andreas Metz (Switzerland), Maria D. Papademetriou (UK), Patrik Persson (Sweden), Felix Scholkmann (Switzerland), Kouichi Yoshihara (Japan)

2012
Allann Al-Armaghany(UK), Malou Friederich-Persson (Sweden), Tharindi Hapuarachchi (UK), Benjamin Jones (UK), Rebecca Re (Italy), Yuta Sekiguchi (Japan), Ebba Sivertsson (Sweden), André Steimers (Germany)

2013
Allann Al-Armaghany (UK), Gemma Bale, Alexander Caicedo Dorado (Belgium), Luke Dunne

As pointed out earlier the first society proceedings were published by Plenum Press.[10,11] However, there has been some confusion about the total number of proceedings published due to different publishers' mistakes using two different names. Some of the first meeting proceedings were published under the Library of Congress Cataloging title of "International Symposium on Oxygen Transport to Tissue" rather than the official title of "International Society on Oxygen Transport to Tissue." Since the two titles are listed separately the uninformed might not be aware of both sets of proceedings and some libraries do not have all of the volumes.

At the 25th Anniversary it was approved by the Executive Committee and the membership-at-large to proceed with arrangements to establish a Journal for ISOTT with Plenum Press.

Many attempts to start a journal have failed for various reasons however we are still active and working with several publishers to develop a society journal. Because ISOTT remains small in numbers, by choice, most publishers do not feel a journal would be profitable.

The future of ISOTT will be determined by our young and new members, with the dedicated mentoring of our old time membership. It will be important to stay current with new technology and be flexible enough to embrace new directions in the area of oxygen transport to tissue. The vision of ISOTT members will be

critical in guiding this very special international scientific and engineering society through the troubled waters created by politics, religion, and other outside influences.

Referring back to Figure 1, the flow of the Chippewa River after the Shamattawa represents the future of the society. Technologies in sensing and measuring oxygen in normal physiology and pathology in combination with theoretical predictions and analysis are major components. Further studies in the pathology of blood and exploring modern technologies to prevent or diminish the harmful impact of oxygen deprivation to tissue are worthy goals.

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