

The history of tissue engineering

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It is essential to know where we have been in order to make reasonable predictions as to where we are headed. This article represents one person’s recollection of the history of Tissue Engineering [1] and consequently, it will most certainly contain some personal biases. I apologize to any individuals whose significant contributions to the field of tissue engineering that may have not been presented here as a result of my own misunderstanding or oversight. In presenting a historical perspective of the emergence of tissue engineering as a multidisciplinary science, I will include the information concerning the development of the journal “Tissue Engineering” and the formation of the society, both of which have evolved during the last decade. Significant future challenges will be discussed.

The famous painting by Fra Angelico entitled, “Healing of Justinian” depicting the brothers Saints Damien and Cosmos Transplanting a Homograft limb onto a wounded soldier is often referred to as the first historical reference to “tissue engineering”. However, Genesis I:1 “The Lord, breathed a deep sleep on the man and while he was asleep he took out one of his ribs and closed up its place with flesh. The Lord God then built up into a woman the rib that he had taken from the man” [2], may be interpreted as the oldest written reference.

As recently as the 1980’s, the term tissue engineering was loosely applied to the use of prosthetic devices and the surgical manipulation of tissues. In

actuality, a meeting held in the late 1980’s in Keystone, Colorado entitled, “Tissue Engineering”, sponsored by the National Science Foundation had very little to do with the discipline of tissue engineering as it is viewed today. While the meeting did emphasize efforts to manipulate living tissues and potentially combine them with prosthetic materials, the actual generation of new tissue utilizing biologics, either alone or in combination with appropriate scaffolding material was not a focus of the meeting.

The roots of Tissue Engineering, as a modern scientific discipline, dedicated to the generation of new tissue using the principles of engineering in combination with an understanding and application of the biologic sciences, are deeply seated in Boston. To my knowledge, the first recorded use of the term Tissue Engineering, as it is applied today, was in a published article entitled, “Functional Organ Replacement: The New Technology of Tissue Engineering” [3] in “Surgical Technology International” in 1991.

The early years

A pediatric orthopedic surgeon at the Children’s Hospital, W. T. Green, M.D., undertook a number of experiments in the early 1970’s to generate new cartilage using chondrocytes seeded onto spicules of bone and implanted in nude mice. Although unsuccessful,

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he correctly concluded that with the advent of innovative biocompatible materials it would be possible to generate new tissue by seeding viable cells onto appropriately configured scaffolds. Several years later, Drs. Burke and Yannas of the Massachusetts General Hospital and M.I.T. collaborated in studies in both the laboratory and in humans to generate a tissue-engineered skin substitute using a collagen matrix to support the growth of dermal fibroblasts. Dr. Howard Green later transferred sheets of keratinocytes onto burn patients, while Dr. Eugene Bell seeded collagen gels with fibroblasts, referring to them as contracted collagen gels. All of these examples represent seeds of the new discipline now known as Tissue Engineering.

Possibly the key point in the birth of this emerging field was in the mid-1980's when Dr. Joseph Vacanti of the Children's Hospital approached Dr. Robert Langer of MIT with an idea to prospectively design appropriate scaffoldings for cell delivery as opposed to seeding cells onto available naturally occurring scaffolds having physical and chemical properties that could not be manipulated, thus resulting in unpredictable outcomes. Dr. Vacanti designed and implemented extensive studies to generate functional tissue equivalents utilizing a branching network of synthetic biocompatible/ biodegradable polymers configured as scaffolds seeded with viable cells. Although the most cited manuscript describing this new discipline may be the article published in *Science* by Langer and Vacanti [4], the original article describing the new technology was published a full five years earlier in 1988 in *Archives in Surgery* [5], as a keynote presentation given at the meeting of the American College of Surgeons in 1988.

Hoping to explore and define the potential of this new field, a number of centers have been organized in the United States and Europe. While the vast majority of these efforts are offshoots of those based in the Boston area, several arose spontaneously. Among the first significant efforts outside of Boston were the development of the Pittsburgh Tissue Engineering Initiative (PTEI) in the early 1990s organized by Peter Johnson, the Cardiovascular Tissue Engineering effort under the direction of Dr. Robert Nerem at Georgia Tech, laboratories overseen by Drs. Antonios Mikos and Larry McIntire at Rice University in Houston, and an effort established at UMass Medical School by Dr. Charles A. Vacanti. Outside of the United States, Dr. Julia Polak, a pathologist and stem cell biologist in London, spearheaded an effort in Tissue Engineering

at the Imperial College and organized a British-based society that developed a loose association with the Tissue Engineering Society (TES) that had previously incorporated in Boston. In the mid-to late-1990's, Dr. Una Chen began conducting tissue engineering and stem cell studies in Giessen, Germany. Dr. Clemente Ibarra founded laboratories for tissue engineering at the National Institute for Rehabilitative Medicine in Mexico City and organized the Mexican Tissue Engineering Society. Dr. Wolfgang Pulacher opened a laboratory for tissue engineering in Innsbruck at the Leopold Institute. During this period, the creation of laboratories and the development of a tri-state effort in Germany, Switzerland, and Southern France were spearheaded by Drs. Raymund E. Horch and G.B.Stark at the University at Freiburg. Their efforts culminated in the formation of a Tissue Engineering Society in Germany, and ultimately, in Western Europe. By the late 1990's Dr. R. Hetzer, a cardiovascular surgeon at the University of Berlin, and Dr. Christof Brelsch, a liver transplant surgeon in Hamburg, established collaborations with the Children's Hospital in Boston, as did a group at Kyoto University headed by Dr. Koichi Tanaka.

In Asia, Dr. Minora Ueda of Nagoya University established a large tissue engineering effort in Japan, and organized the first meeting of the Japanese Tissue Engineering Society (1997) in Nagoya. The first Chinese tissue engineering effort, sponsored by the Chinese government, was founded by Dr. Yi Lin Cao in Shanghai. Another by Dr. Steven Kim in Seattle, and at the University of Washington under the direction of Dr. Buddy Rattner, and in Toronto, under the direction of Michael Sefton

By the mid to late 1990's, tissue engineering efforts including one at Yale University, established by Drs. Chris Brewer and Mark Saltzman, were springing-up in virtually every developed country in the world and several privately funded ventures in Tissue Engineering began to arise.

Development of an organizational structure

In 1994 there was felt to be sufficient momentum to organize a society and to establish a journal dedicated to scientific interactions and the communication of high quality scientific presentations and publications.

The society

The Tissue Engineering Society (**TES**), conceived of and founded by Drs. Charles A. and Joseph P. Vacanti in Boston in 1994, was officially incorporated in the state of Massachusetts on January 8, 1996. The original Governing Board of seven members included the founding Presidents, Drs. Charles and Joseph Vacanti, as well as Dr. Robert Langer of MIT, Dr. Joseph Upton of the Beth Israel Deaconess Medical Center and Harvard Medical School, Dr. Tony Atala of Children's Hospital, Mark Randolph of the Massachusetts General Hospital and Linda Cina of MIT. It was decided that the Society was to be an international Society and that meetings would initially be held on a biannual basis. Over the next decade, in conjunction with the Asian and European Societies, TES would evolve and reorganize to become TESI and then **TERMIS**, the Tissue Engineering and Regenerative Medicine International Society, by 2005. Dues for membership in the original Society in 1996 were \$40 for physicians and research scientists and \$15 for residents and students. Peter Johnson and David Smith were instrumental in helping launch TES, with David providing legal counsel, gratis. To date, eight meetings have been held. Initially the meetings were bi-annual with the first three being held in Orlando. Subsequent meetings were held at various international locations on an annual basis. The inaugural meeting of the international Tissue Engineering Society (TES), organized by Charles and Linda Vacanti, was held in December, 1996 at the Lake Buena Vista Hotel in Orlando, Florida. Attendance was approximately 300 people, representing thirteen countries. At the end of the first meeting, the founding President, Dr. Charles A. Vacanti was elected as the first elected President of the Society. The next two meetings of the TES were also held at the same location in Orlando, renamed the Wyndham Hotel in 2000. Initially, somewhat of a "Mom & Pop" organization, the inaugural meeting was organized to a great extent by Linda K. Vacanti, who also hosted the first two meetings and assumed responsibility for all the administrative functions. All submitted abstracts were read and evaluated Drs. Charles and Joseph Vacanti. Subsequent meetings held annually in different locations had increasing professional input and organization. Successive elected presidents of the society were, Joseph P. Vacanti, MD, of Boston (the other founding father) in 1998, Peter Johnson,

MD, of the Pittsburgh Tissue Engineering Initiative in 2000, Robert Nerem, Ph.D. of Georgia Tech in 2002, and Alan Russell of University of Pittsburgh in 2004.

As previously mentioned, Drs. Horch and Stark of Freiburg, Germany encouraged the formation of a European tissue engineering society (ETES) with the assistance of Dr. Julia Polak of the Imperial College in London and founder of the British Society, and Dr. Ranieri Cancedda of Genoa, Italy, who had spearheaded the formation of an Italian society. The following year, 2001, the TESI meeting was held in Freiberg, Germany, in combination with the fledgling ETES. At the meeting hosted by Drs. Stark and Horch, Dr. Cancedda was elected President of the ETES. Subsequently, the European Society, loosely associated with the London-based British Tissue Engineering Society, and aligned with the TESI, ultimately as a European continental branch in a similar fashion to the Asian continental branch of the TESI.

The Japanese Tissue Engineering Society was organized in 1977 a few years after that of the the international (TES) by Dr. Minoru Ueda with its first meeting held in Nagoya, Japan. Dr. Yi Lin Cao then formed the Chinese Tissue Engineering Society and Shanghai-based Tissue Engineering Center. These societies formed a loose association, and aligned as the Asian branch of the international Tissue Engineering Society, then referred to as **TESi**.

In 2002 the meeting of TESI was held in Kobe, Japan in conjunction with the Japanese Tissue Engineering Society (JTES) and the Asian continental branch of TESI. Dr. Ueda, president of both the JTES and the Asian branch of the TESI hosted the meeting.

As a consequence of the SARS epidemic, the 2003 meeting of TESI, originally planned to be held in Toronto, was moved to the location of the first three TES meetings; that is, Orlando. The meeting, hosted by Dr. John Davies and other scientists from Toronto, was presided over by the fourth elected President of now the TESI, Dr. Robert Nerem of Georgia Tech. Dr. Alan Russell from the University of Pittsburgh and the Pittsburgh Tissue Engineering Initiative was elected at that meeting as the fifth President of the international Society. A decision was made by the Governing Board of TESI to re-emphasize that the future direction of the Society should reflect its original intent. The Society, originally formed as an international Society, founded in North

America, would have worldwide representation. It would continue to support international meetings as well as coordinate meetings in North America. Following the meeting, a recommendation was made to explore a more formal merging of what had been continental branches of the former TESI. To reflect the evolution of the discipline, which had expanded to include regenerative medicine, the merged entity was renamed the Tissue Engineering Regenerative Medicine International Society (TERMIS).

In 2004 the meeting was held in Lausanne, Switzerland. The following year, Dr. Yi Lin Cao hosted the largest TESI meeting to date, in conjunction with the Chinese Tissue Engineering Society, in Shanghai, China. More than 600 international attendees participated with more than 900 registered attendees.

In June of 2005, it was announced that ETES was being recognized as a formal continental chapter of the Society. Dr. Russell, the 5th President of TESI, continued as President of TERMIS for an anticipated two years. It was agreed that he would be followed by Dr. Jöns Hilborn, who had been President of the European Continental branch (ETES), as the sixth President of the mother Society. A similar approach is now being explored for what is currently the Asian continental branch. The ultimate goal remains the same; that is, to achieve a worldwide organization, as originally envisioned.

Ten years after being established, the structure of the society is certainly more well-defined, more efficient as a business, and has a more sophisticated system of governance. Its name has been changed to reflect a broader scope. In spite of these changes, its goals appear to be consistent with those initially defined a decade ago by the founding board. The society was to be an international society that would “continually encourage and promote the exchange of information in the field of Tissue Engineering through education, research and the dissemination of information useful to the individual and beneficial to mankind”. It seems as though we have come full circle to where we started in 1996.

The journal

With the formation of the Society, the founding Board of Governors felt that it was important to have an effective means by which to exchange scientific

information and freely express new ideas. The journal “Tissue Engineering” was founded in 1994 by Drs. Charles A. Vacanti of the Massachusetts General Hospital and Harvard Medical School, and Antonios Mikos of Rice University. Its Editorial Board was composed of an international balance of physicians and scientists, and its administration on a daily basis was largely done by Linda K. Vacanti.

Initially, manuscript submissions were aggressively solicited. In spite of the large, formal editorial board, a high percentage of the original manuscripts were reviewed by Drs. Mikos and Vacanti. For a decade, Linda Vacanti and Carol Lofton dedicated a tremendous administrative effort to organizing the structure of the journal, chasing-down and “hounding” reviewers for comments, keeping authors informed of the status of their manuscripts and proof-reading all of the articles. It was a thankless job, for which I would now like to publicly thank them. Their dedication, judgment and effectiveness have been stellar and the journal owes much of its success to their efforts.

Mary Anne Liebert Publications has produced a very professional, extremely well-managed journal, and has been a delight to work with. Over a period of ten years, the journal has grown in stature and respect to now command an international audience and an impact factor of greater than 3.

I would like to thank Patrea Pabst for her dedication in writing patent updates for the journal over an extended period of time. Her articles have been interesting, insightful and timely.

Michael Lysaght, Ph.D. has also generously provided legislative and business updates, for which I would like to express my gratitude.

In 2000, the editorial board was modified as editorial offices were added in London and Tokyo. Dr. Julia Polak and Dr. Yasuhara Noishiki were named Associate International Editors in the London and Tokyo offices respectively. In 2003 Minora Ueda replaced Dr. Noishiki and, in 2004 Dr. Teruro Okano was named as the Asian Associate Editor. At the end of 2003, Dr. Vacanti stepped down as a founding editor. Dr. Peter Johnson then assumed responsibilities as co-editor of the journal with Dr. Mikos. The membership of the editorial board continues to evolve to allow input from young, emerging scientists. I would like to acknowledge and thank Dr. Johnson for his efforts on behalf of the journal and the Society. I would also like to express

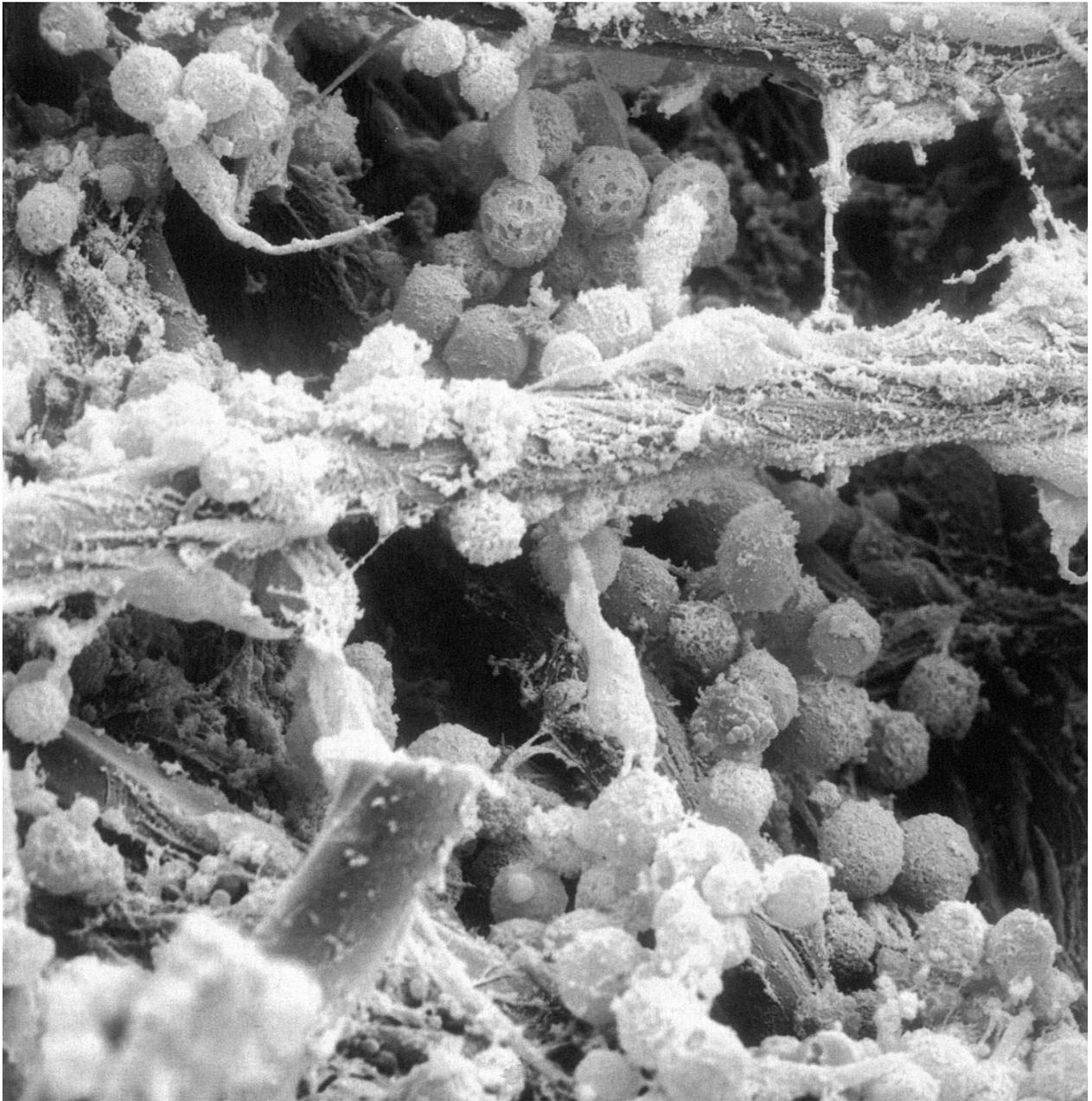


Fig. 1a Scanning electro micrograph of cells seeded onto synthetic scaffold composed of a random array of polyglycolic acid fibers.

my tremendous admiration and thanks to Antonios Mikos. My co-editor for almost a decade, who continues to serve as editor of the journal. I could not have worked with a more reasonable, delightful, organized, dedicated and objective person.

To date, the journal has retained the original name “Tissue Engineering”, which I believe accurately reflects the scope of this specialized, multidisciplinary

field. Significant efforts now exist to merge the fields of tissue engineering and regenerative medicine, as evidenced by the changes in name and scope of the Society. Since both fields represent multidisciplinary efforts in medicine with many area of overlap, arguments to merge them seem obvious. I do however believe that tissue engineering is a science devoted to the generation of new tissue by



Fig. 1b Photograph of infamous mouse with the human ear, depicting new tissue-engineered cartilage generated in the shape of a human ear.

employing the principles of engineering in combination with the application of certain biological principles. Although regenerative medicine and tissue engineering share a common goal, that is, restoration of tissue or organ function, the means in which the goal is accomplished can be very different. Many facets of regenerative medicine may be accomplished by applying biologic principles without any consideration of any of the principles of engineering. Alternately, one may be able to engineer tissue with new functional attributes unrelated to a regenerative process. For these reasons, I do believe that the two fields are distinct, although an interactive relationship is beneficial to both efforts. At this time, I continue to believe that a journal dedicated specifically to tissue engineering is still quite appropriate.

Tissue engineering and the public arena

Tissue engineering was catapulted to the forefront of public awareness with the airing of a BBC broadcast exploring the potential of tissue-engineered cartilage when it broadcast images of the now infamous “mouse with the human ear” Fig. 1, fondly referred to as auriculosaurus, from the laboratory of Dr. Charles Vacanti at University of Massachusetts Medical Center. Examples of what has now become known as tissue engineering were all based on the

same premise, that new functional replacement tissue could be generated from living cells seeded onto appropriately configured scaffoldings. In the example of engineered skin, dermal fibroblasts grew on naturally occurring scaffolds composed of collagen fibers. In the example of cartilage, viable chondrocytes were seeded onto porous polymer fibers and configured in the shape of the desired tissue. In 1991, a young patient with Polands Syndrome, a congenital malformation of the rib-cage and absence of a sternum, became the first human to receive a tissue-engineered implant composed of a synthetic polymer scaffold implant seeded with autologous chondrocytes, intended to replace his absent sternum at the Children’s Hospital in Boston. The procedure was performed by 3 of the original 8 members of the founding governing board of the Tissue Engineering Society, Dr. J. Upton and Drs. J. and C. Vacanti. In 1998 a similar approach was utilized to replace avulsed distal phalanx on an industrial worker who had experienced a traumatic amputation of his thumb at UMass Medical Center by Drs. J. Shuffelberger and C. Vacanti.⁶ The implant, composed of porous coral seeded with the autologous periodical derived cells obtained from a radial bone biopsy, was placed over the proximal phalanx of his injured thumb. Dr. Toshiharu Shin’oka of the Department of Cardiovascular Surgery, The Heart Institute of Japan, Tokyo Women’s Medical University, applied this discipline, on a larger scale,

to humans when he generated tissue-engineered pulmonary arteries [7]. These examples supported the tremendous potential in generating new replacement parts for humans.

Future challenges

In spite of scientific progress, there are few examples of the human application. Two potential explanations for this may be 1) problems associated with “scale up” and 2) cell death associated with implantation. Large numbers of cells are needed to generate relatively small volumes of tissue. To ultimately be effective in humans, it will be necessary to generate relatively large volumes, starting with very few cells. Mature cells, expanded *in vitro*, lose efficacy. Cell implantation and its associated vascular disruption results in a relatively hypoxic environment and cell death. The potential for different cell types to be expanded *in vitro* and survive a relatively hostile environment, at the time of implantation is now being explored. To be effective, cells should be easily procured, effectively expanded *in vitro*, survive the initial implantation, be accepted as self; that is, not recognized as foreign, and function normally and not become malignant. In addition, it would also be quite convenient if no moral concerns or questions were generated as a result of the cell type used.

There is a considerable debate concerning different cell sources. Mature cells have a relatively high oxygen requirement and a low potential for expansion (scale up). Alternatively, there are several sources of “immature” cells. Immature cells, commonly referred to as stem or progenitor cells may be classified as embryonic in origin or adult somatic stem cells. It is my opinion that many previously described adult stem and progenitor cells have a common origin.

Embryonic and adult stem cells may have very similar potentials to develop into the different cellular elements necessary for effective tissue regeneration. Alternatively, the differences may be significant. Embryonic stem cells have been postulated to retain a greater ability to produce healthier tissue. Again, this may or may not be the case. At this point in time, there is little evidence that embryonic stem cells can be consistently driven to form only the cell type needed for the tissue to be engineered.

Being derived from allogeneic cells, embryonic stem cells have the associated problem of rejection.

It is my belief that some forms of tissue-specific adult stem cells may represent Mother Nature’s repair cells. With the development of appropriate tissue-specific scaffoldings and the use of the optimal cell type, I believe that physicians and scientists will ultimately be able to repair or replace any tissue in the human body which is injured or damaged as a result of disease or trauma. Studies involving the use of stem cells and mature cells, in combination with genetic manipulation and studies determining the efficacy of cellular delivery systems and scaffoldings, should enable rapid progression to human treatments [8]. In a recent article published in the New England Journal of Medicine it was demonstrated that the transplanted heart in a patient was populated by a significant number of his own cells after a relatively few years [9]. I believe that this represents a type of regenerative medicine if indeed the transplanted heart is viewed biologically as a scaffolding in which the transplanted cells ultimately die and are replaced by one’s own repair cells. It is my belief that exploring the use of appropriate vehicles and cell types will ultimately lead to resolution of the symptoms of strokes such as paralysis, and may help reverse the symptoms associated with such central nervous system diseases as Parkinson’s Disease and Alzheimer’s Disease. At some point in the future it may be possible to remove organ-specific cells from patients with certain diseases, genetically manipulate them *in vitro*, and return them to the patient in a manner that will allow for the development of a “mosaic tissue” or tissue consisting of the patient’s own diseased cells, as well as his own genetically repaired cells. It is even conceivable that such an approach may help re-populate specific organs and enable partial recovery in patients with certain forms of Muscular Dystrophy or even patients having trisomy 21, Downe’s Syndrome. I also believe that, if indeed adult stem cells are Mother Nature’s repair cells, that they may have the potential to become malignant when environmental cues are significantly altered. If the environment is so severely disrupted that the somatic stem cells lose their local environmental cues and their template for reconstruction, they may, under certain conditions, remain in their high replication phase and not progress to maturity. Until recently, it was believed that only cancer cells expressed oncogenes, however, more recent studies indicate that during a phase of high replica-

tion, the expression of such markers, for a period of time, is normal. It is my belief that instances of repetitive or significant injury, which result in the loss of environmental cues to the repair cells, may cause these cells to undergo a time of very high degree of multiplication, then lose their environmental cues and not mature. In this state of high multiplication, the cells will express oncogenes and may indeed become malignant. In this respect, cancer cells may represent the natural repair process of the body that has gone awry. They may be small enough to be transported *via* the lymphatic system which generally limits the entry of larger, more mature cells and metastasize to distant sites. At this time there is not sufficient evidence to verify this hypothesis; however I believe that it is indeed an internally consistent model that may explain both the process of repair and repair gone awry, or cancer. As such, the study of the replication and maturization of these cells may lead to significant advances in the treatment of various cancers.

In conclusion

The development of the field of Tissue Engineering has been interesting, to say the least. It has also been challenging, gratifying and memorable. Although the number of multidisciplinary technologies currently being studied in medicine and the biologic sciences appears to be overwhelming and unrelated, it is my belief that the accumulation of such knowledge will ultimately culminate in the clarification of one central process responsible for development, repair and regeneration of any organ system, as well as the mechanism and potential treatment for cancer.

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I would most importantly like to thank my wife of 33 years, Linda K. Vacanti, who not only supported me in these efforts, but served as the Administrator of the journal for almost a decade and of the Society for 5 years.

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I would like to thank the governing boards of the Society and editorial board of the journal for the tremendous amount of work to make these endeavors successful. Most importantly, I wish to thank all of the members of the Society, internationally, for their support and the research scientists who contribute as authors and subscribers to the journal.

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