

THE ART AND SCIENCE OF ANTI-AGING MEDICINE

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Gerontology, a discipline in medicine dealing with the science of aging, originated 30 years ago with the establishment of new methods for analysis in genetics and microbiology. It also deals with the introduction of new therapeutic concepts resulting from medical and pharmaceutical research. Anti-aging is thus a recent medical discipline and is discussed rather controversially because it is frequently misunderstood. It is repeatedly misrepresented by the media and often practiced by laypersons without any profound knowledge about the subject matter. Moreover, it is most often practiced without scientific basis. This is why anti-aging is being discredited as a field of study and research. Till now, the focus is mainly on diseases which develop as people age. Despite great efforts, we still have only limited knowledge about the reasons behind the aging process. Thus, gerontology focuses almost exclusively on the therapy of diseases that come with age, but we are unable to offer any preventive care for such diseases.

Aging is not a disease

Knowledge of the most common causes of death in the aged individuals, such as cardiovascular diseases, strokes or cancer, does not help us in any way to understand the physiology of aging.

The study of age-related diseases still dominates our research and is mistaken to be the same as doing research on anti-aging. We all age, but this does not mean that all of us will develop diseases as we age and die of these diseases. There are a lot of very healthy old people around in the world without any signs of tumors, cardiovascular diseases or dementia. All of us have to die eventually. However, is the inevitability of death a result of aging per se or is it because some organs possibly age faster than others and thus somehow limit a person's age expectancy? Some healthy old people live up to 100 years of age whereas others die 20, 30, 40 years earlier.

What distinguishes aging processes from disease processes?

Aging processes occur in all living beings, once they have reached a certain stage regardless of the species i.e. after the reproductive phase of development. Disease processes occur independently of certain stage and before as well as after the reproductive phase.

Facts on life expectancy

Around 1900, the average life expectancy was 49 years. Since then, there has been an enormous increase of life expectancy. Currently, the average life expectancy is 76 years. (1) It is interesting to note, that the same increase in life expectancy occurred from the time of the Romans up to 1900. In ancient Rome, people died at the average age of 22. The dramatic increase in life expectancy by 54 years from ancient Rome time up to 1997 can be attributed to better hygiene. Current research suggests that with the help of modern medicine, the average life expectancy will only further increase by a maximum of 15 years to an average of approximately 90 years of age (2). This increase of 15 years would mean fighting all kinds of illnesses, but would not take into consideration normal healthy older people. We know, that the maximum lifespan is 125 years simply because no one has ever lived longer. This means that there is only a window of 35 years (from 90 years to 125 years) in which anti-aging medicine could be applied.

What is anti-aging medicine?

Anti-aging medicine is a new trend, which was primarily based on hormonal substitutions in women and which has since been extended to hormonal substitutions in men. However, we should keep in mind that life is much more complex than we sometimes would like it to be. Money will never buy you happiness. The same is true of hormones or vitamins or whatever you think will help you stay young and healthy. Sometimes, too much of one thing is as bad or even worse than nothing at all.

We have to keep things in balance, and this balance should include the following points:

- A healthy lifestyle without excesses of any kind. As mentioned above, too much of anything can be as detrimental as too little. The Roman principle is still valid for our lives today: “dosis facit venenum,” which means: “It is the dose that makes the poison.”
- Regular and moderate exercise to keep tissue well nourished by good blood circulation.
- If hormones are necessary, as in the case of aging and gradual decline in hormone homeostasis, hormone substitution can help to sustain the vigor of the body.
- Stem cells for tissue and cell renewal in the future .

Just as seeds need good soil and optimal conditions to thrive, stem cells need healthy tissue and hormones to flourish. 🌱

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THE POLITICS AND ETHICS OF ANTI-AGING SCIENCE

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Several years ago, an international group of 51 biogerontologists (scientists who conduct research on the biology of aging) launched a war of words to discredit a burgeoning commercial and clinical anti-aging medicine movement. They issued a lengthy consensus position statement asserting that there are no effective anti-aging measures, accompanied by an article in *Scientific American* entitled “No Truth to the Fountain of Youth.” They also arranged for this position statement to be published in scientific journals throughout the world.

The biogerontologists’ enemy in this war is what they regard as the pseudoscience of practitioners and entrepreneurs that purvey hormone injections, special mineral waters, and other services and products purported to combat the effects of aging. One of their prime targets is the American Academy of Anti-Aging Medicine (A4M) which board-certifies “longevity” practitioners and claims 12 000 members in 65 nations. A4M’s website displays numerous advertisements for anti-aging products and services, clinics, and practitioners. It also has an “A4M Longevity Store” where memberships in A4M are sold as well as books authored by the organization’s president, such as *Ten Weeks to a Younger You*.

Yet, even as biogerontologists are attacking the contemporary anti-aging medicine movement, many of them are themselves trying to develop interventions that will slow or arrest the fundamental processes of aging dramatically. In fact, an unintended consequence of the biogerontologists’ attacks on anti-aging medicine is that they are diverting attention from the potentially radical societal implications of their own anti-aging research efforts — implications that should be widely discussed in nations throughout the world.

Why the War on Anti-Aging Medicine?

What is this recent effort to discredit anti-aging medicine about? After all, measures promoted as anti-aging interventions have been part of human culture and societies for millennia (including a Taoist program for prolonging life in the third century B.C. in China) with criticisms of them waxing and waning over the centuries.

On the surface, the 51 scientists' position statement and associated articles can be seen as part of a larger public health effort to educate health professionals and the public regarding harmful and misleading aspects of anti-aging interventions and claims. However, the war on anti-aging medicine is an attempt by established biogerontologists to preserve their hard won, but still fragile, scientific and political legitimacy which took many years to achieve. They also try to maintain and enhance funding for their research on the basic biological mechanisms of aging. As such, it is "boundary work" that parallels disputes in many other areas of science in which rhetorical demarcations are employed to maintain legitimacy and power.

The Ongoing Struggle for Legitimacy

Throughout most of human history, efforts to achieve longevity (significant extension of maximum life span and average life expectancy) have been viewed with great skepticism and have not been regarded as serious science. As Betty Lockett's history of U.S. biogerontology put it only 20 years ago: "Those who would study aging in order to retard or halt the process have been considered to be on the fringe of biomedical research, looking for the fountain of youth—a marginal area with so little backing from the scientific community." The present effort of biogerontologists to downplay "the fountain of youth" can be best understood in this historical context.

However, the creation of a National Institute on Aging (NIA) at the U.S. National Institutes of Health (NIH) in 1974, provided biogerontology with the kind of institutionalization that confers scientific stature and power, legitimating it both as more of a "mainstream" subject for biomedical research and also as an appropriate area to invest sizable amounts of public funds. Since then, a number of important scientific frontiers have been opened up in biogerontology.

Nonetheless, the image of biogerontology as a legitimate and mainstream scientific pursuit is still vulnerable enough to be threatened by the anti-aging medicine movement. The position statement by the biogerontologists acknowledged, "Our concern is that when proponents of anti-aging medicine claim that the fountain of youth has already been discovered, it negatively affects the credibility of serious scientific research efforts on aging." Similarly, the founding director of NIA, Dr. Robert N. Butler, recently observed, "Unfortunately, anti-aging medicine is often confused with serious research. Consequently, public and private philanthropic organizations are less interested in funding serious aging research." As these comments imply, the war on anti-aging medicine is being waged primarily so that the image of research on aging will not become blemished once more.

The Pursuit of Prolongevity

Simultaneously with this attempt to establish a boundary between anti-aging medicine and “legitimate” research on aging, the efforts of many biogerontologists to achieve dramatic anti-aging interventions continue unabated, encouraged by public scientific institutions like NIH. In 1999, for example, two NIH institutes jointly convened a working group of over 50 scientists to explore the significant possibilities for applying to humans the prolongevity affects that have been achieved in caloric restriction experiments with laboratory animals. The group produced a substantial agenda of opportunities for research on human implications, including the goals of slowing fundamental processes of aging and extending maximum human life span. This fit right in with one of the priorities declared by NIA in its current official strategic plan which is to “unlock the secrets” of aging, health, and longevity, including the identification the of factors that “slow the clock” of aging. In line with this goal, some biogerontologists are now working on the development of pills that could mimic the anti-aging effects of dietary caloric restriction.

The accomplishment of this agenda to slow the fundamental processes of aging — to achieve decelerated aging. This would not only delay age-associated diseases and disabilities, but also greatly increase both average life expectancy and maximum life span beyond the prior experience of our species. Biogerontologist Richard Miller of the University of Michigan suggests that an effective anti-aging intervention to achieve decelerated aging “might increase the mean and maximal human life span by about 40 percent, which is a mean age at death of about 112 years for Caucasian American or Japanese women, with an occasional winner topping out at about 140 years.”

A more radical prospect is championed by other biogerontologists, led by Aubrey de Grey of the University of Cambridge. They hope to achieve arrested aging by continually restoring vitality and function through reversal of the processes of aging as they occur in adults, thereby removing the damage inevitably caused by basic metabolic processes. De Grey and his colleagues expect that substantive progress towards this objective will be feasible within about a decade, and he asserts that it is “inevitable that we will eventually achieve a 150-year mean longevity.”

Confronting Implications of “The Impossible”

As improbable as any of these aspirations may seem at present, developments in science, such as the cloning of mammals, can catch society unaware by accomplishing what seemed to be “the impossible.” Consequently, it is none too soon to undertake anticipatory deliberations concerning issues generated by the potential consequences of the anti-aging interventions being pursued by biogerontologists.

If dramatic increases in healthy life expectancy and life span become feasible, how should the interventions that they achieve them be allocated in society? Serious ethical issues would be created if the interventions were not universally available, but allocated in accordance with wealth, social and political status, ascribed “merit,” or some other distinguishing criteria. Alternatively, if access to effective anti-aging interventions were unlimited, radical societal changes would take place in the nature of the labor and housing markets, family life, politics and public policies, the law, and almost every social institution.

These and other potential consequences of the effective anti-aging interventions have much more profound and far-reaching implications than any other current biomedical policy issues, such as the ethics of human cloning. If biogerontologists succeed in their aspirations to decelerate or arrest aging, the consequent transformations in the nature of individuals and their collective life may well be radical. Yet, these ideas have rarely been addressed to date, and not in forums that reach a wide public.

In nations throughout the world, we need to begin widespread public discussions of the implications of achieving decelerated and arrested aging. Public institutions such as the U.S. NIH are already supporting anti-aging scientific research that could lead to such outcomes. Now, it is time for biogerontologists who are engaged in this research to undertake more active leadership in helping the public to understand their goals and to deliberately consider the implications of their fulfillment. Through such discussions we may be able to shape wisely the future of developments in anti-aging science and their social consequences. In the long run, leadership by biogerontologists in such an effort would be an even greater service for all of us than their current war on contemporary anti-aging products and therapies. 🌱

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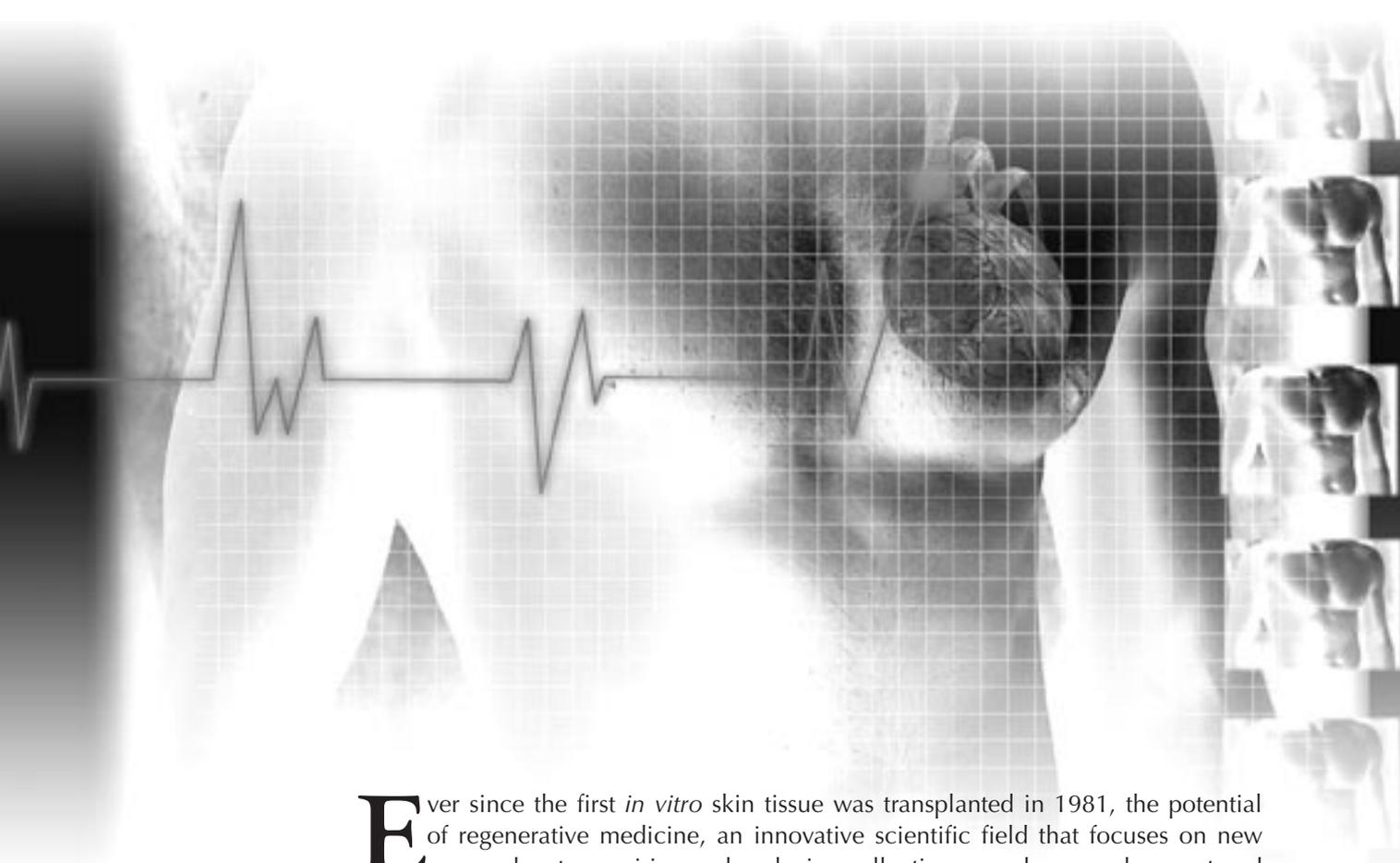
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REGENERATIVE MEDICINE CURRENT STATUS AND PROSPECTS

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Ever since the first *in vitro* skin tissue was transplanted in 1981, the potential of regenerative medicine, an innovative scientific field that focuses on new approaches to repairing and replacing cells, tissues and organs, has captured the imagination of many physicians and scientists. The technologies for engineering tissues are developing rapidly, with the ultimate goal of delivering new therapies as safely and efficiently as possible. The importance of the relatively new frontier of regenerative medicine is embodied in the unprecedented need of patients from all around the world.

Regenerative medicine fosters multidisciplinary interaction between scientists in the fields of biomedical and chemical engineering, cell and molecular biology, biochemistry, physiology, materials science, nanotechnology, genomics, drug delivery, proteomics, surgery and medicine. Regenerative medicine focuses on a wide range of engineered tissues with the aim of making a lasting impact on conditions ranging from congenital abnormalities to acquired pathologies, such as infection, tumors, trauma and chronic diseases.

Why Regenerative Medicine?

Organ transplantation was a major advancement in medicine in the 20th century. However, the demand for transplantable organs consistently outstrips the supply. For example, the number of patients awaiting transplants of all types increases by approximately 20% each year, but the number of donors has remained small, at under 4.0% of the potential donors; the number of patients wait-listed for transplants increased by over 50,000 in the last decade, from about 32,000 to 87,000, while the number of transplants performed remained flat at under 15,000 per year; a patient on the transplant list dies every 90 minutes.

The Joint Commission for Health Care Organizations recently declared the shortage of transplantable organs and tissues a public health crisis. The prevalence of obesity, hypertension and diabetes, and the ever increasing aging population, will most likely increase the need for more organs in the years to come. There is about one death every 30 seconds due to organ failure, and the complications and the rejection are also significant problems. The national cost of caring for persons who might benefit from engineered tissues or organs has reached \$600 billion annually. One of the JCAHO's recommendations to meet this impending crisis is to "support the progression of new sciences and technologies that have the potential to narrow the donation gap and decrease the risk of organ rejection."

Regenerative medicine promises to bypass the organ shortage by making the donor and the recipient the same. A biopsy from the patient yields cells that are nurtured in the laboratory to form functional tissues and organs that can then be implanted back into the patient. The use of a patient's own cells eliminates the risk of rejection that accompanies traditional organ transplantation. The body has a natural healing capability. Regenerative medicine aims to harness this natural healing process by helping cells to grow, divide and differentiate *in vitro* for implantation, or by stimulating progenitor or stem cells to repair tissues in the body. Regenerative medicine brings hope to patients with conditions like diabetes, cancer, or muscle disease, and to those who suffer tissue or organ damage due to trauma or congenital abnormalities.

The Potential of Regenerative Medicine

New knowledge in cellular, molecular and physiological processes sets the stage for revolutionary treatments of many human medical conditions. Regenerative medicine addresses the shortage of human organs and tissues by using cells for therapy (i.e., pancreatic islet cells, heart cells, nerve cells), engineered tissues for therapy (i.e., cartilage, bone, muscle) and engineered organs for therapy (i.e., kidney, liver, bladder, uterus, vagina, trachea, esophagus, heart valves, blood vessels).

This is possible due to several key advances, including the development of systems that can reliably nurture cells as they grow and divide; the discovery of growth factors that foster cell proliferation *in vitro*, and fabrication of biomaterial scaffolds for tissue generation in three-dimensions.

Regenerative medicine is a composite term that encompasses many scientific and medical disciplines that ultimately come together to make distinctive contributions to the new technologies and therapies.

Components of Regenerative Medicine

The engineering of new tissues and organs may involve biomaterials alone, wherein the body's natural ability to regenerate is used to orient and direct new tissue growth, or the use of cells with biomaterials. Cells, as fundamental building blocks, are an important component of regenerative medicine whether used with scaffolds to engineer implantable tissues or injected to achieve desired cellular function. Reliable cell culture and expansion systems are required to be able to utilize cells for therapeutic applications. Cells from various sources have been studied to achieve optimal therapeutic outcomes. Targeted modification of cells in culture allows for the achievement of better performance for specific clinical applications.

Research has expanded to include stem cells as a promising source for both the quality and the quantity of tissue needed to engineer complete organs. Recent discoveries of the potential sources of undifferentiated stem cells in various tissues, as well as techniques for expanding them in the laboratory, further extend the applications for tissue engineering. Stem cells are an attractive cell source, since they possess the ability to become various tissue types. Systems for stem cell isolation, expansion and differentiation for guiding the cells into numerous cell types, including bone, fat, muscle, liver, pancreatic, nerve and endothelial cells, have been developed and optimized.

Biomaterials are an important element in virtually every application in regenerative medicine. They serve as delivery vehicles for cells (scaffolds that support engineered organs until they can function alone) and promoters of tissue regeneration. Biomaterials used in regenerative medicine must be biocompatible, be made to fit a wide range of structural and functional parameters, as one application may require adequate space to accommodate a large quantity of cells, ingrowing nerves and blood vessels, while another may be constructed to allow easy injection through a needle. To guide the cells in forming functional tissue structures *in vivo*, a careful selection of biomaterials and three-dimensional scaffold fabrication is necessary. The biomaterials used in scaffolds must be designed to degrade over a timeline that is appropriate for the particular tissue or organ they are supporting. Of course, the degradation products must exit or be incorporated into the body without causing negative reactions.

Enhancement of regenerated cell, tissue and organ have been implemented to achieve improved function by new technologies which include controlled and targeted delivery of therapeutic agents to specific cells and tissues; fabrication of functional scaffolds for promoting nerve and vessel formation; development and formulation of novel drug delivery vehicles; immuno-isolation of cells for cell and tissue therapy; and integration of nanotechnology to controlled delivery systems for clinical applications. Bioactive growth factors and macromolecules have also been incorporated into the scaffold system using controlled release technologies. For example, a protein called BMP can be used for enhanced bone regeneration, the growth factor VEGF can be used for new blood vessel formation, and nerve growth factor (NGF) can be used for promoting the reinnervation of tissues.

One of the important components of the engineered cells, tissues and organs is the functional assessment. Confirmation of cellular function prior to and after cell placement on scaffolds is necessary to ensure successful tissue formation *in vivo*. For example, engineered blood vessels, with a major smooth muscle component, must demonstrate the ability to contract and relax just like native vessels. They must respond appropriately to changes in blood pressure and alterations in other variables that affect

circulation (hormones, neurotransmitters, neuromodulators, etc.). Cardiac, smooth and skeletal muscles are all able to contract and relax, but each behaves and responds differently in the body. To engineer tissues that function normally in the target site, it is essential that the normal functional characteristics of each be determined prior to use in a clinical setting. Moreover, safety and efficacy in basic cell, tissue and organ research require clinical translation capabilities.

Clinical Translation

Clinical translation is essential for the efficient transfer of regenerative medicine techniques from the bench to the bedside. A critical component for the dissemination of these new advances to a wide number of patients is the creation of successful good manufacturing practices (GMP) production facilities that can efficiently deliver the therapeutic products health care providers. Industrial support and investor resources are often required for the successful applications of these technologies to patients.

Although understanding of the basic conditions needed to create engineered tissues in the laboratory setting has progressed dramatically, several basic challenges drive the pursuit of tissue and organ production on a large scale. It is necessary to create more efficient ways to enhance cell growth, division and differentiation *in vitro*, and to develop ideal three-dimensional scaffolds that will allow engineered tissues to mimic organ or tissue function while ensuring long-term survival of the engineered tissues. One of the obstacles encountered in applying cell-based technologies is achieving adequate vascularization to large engineered tissues.

In summary, regenerative medicine offers new therapeutic approaches to repairing and replacing cells, tissues and organs to restore normal function. The efforts exerted by scientists with multidisciplinary background may deliver one of the most pervasive impacts on public health in the modern era. 🌐

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