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Medicine, Mortality and Health in the 21st Century

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At the turn of the 20th century doctors could do little for ailing patients other than wait for them to get better on their own or die. Although doctors understood the germ theory of disease, there were no antibiotics to fight infections and anesthetics were still in their infancy. Blood types were discovered in 1901 but widespread collection, typing, storage and dissemination of blood did not occur until World War II. People living in today's environment where antibiotics are commonplace, anesthetics are widely used, and surgery has benefitted from a host of advances have little realization of just how precarious good health was back then and what tremendous strides were made in the 20th century. Prospects for 21st century medicine border on science fiction: tissue regeneration, new organ growth and systems biology are currently the cutting edge of medical science, but may one day be as commonplace as antibiotics and transfusion are today.

Dr. Leroy Hood has written hundreds of scientific papers, participated in numerous biotechnology startups and received many prestigious awards. He also invented four key machines that played prominent roles in modern biotechnology: automated DNA sequencers and synthesizers and automated protein sequencers and synthesizers. Once the genome was sequenced in 2000, Hood quickly realized that further progress would depend upon a deeper knowledge of how genes interact. This is because most cellular processes involve the linking of many genes in complex feedback and feed-forward loops that have cascades of interactions. So Hood and two other scientists co-founded the Institute for Systems Biology (ISB) with the mission of transforming biomedical research by creating and using systems approaches to unravel the workings of complex biological interactions.

One of the basic premises of systems biology is that the reductionist approach normally used in science is inadequate. This is best explained by analogy. If you focused on identifying the engine, seat belts, and other parts of an automobile and learned how each of them worked you still would have no knowledge of how an automobile operates. It is only when you observe the entire system functioning as a unit that its emergent

properties become clear. Systems biology focuses on studying the entire system of biological interactions and understanding the properties emerging from that system. A system is said to be complex if its emergent properties are unpredictable. Living organisms are complex systems. Life is one of the emergent and unpredictable properties of biochemical systems.

Hood says, "Studying the interactions and interplay of many levels of biological information, systems biology will enable us not only to cure complex diseases but also to predict an individual's health and extend the human body's natural lifespan by preventing diseases. The new era of predictive, preventive and personalized medicine – made possible by systems biology – represents a profound shift in the practice of medicine and will reach into many corners of our lives."

More information can be found under the "Intro to Systems Biology" tab on the ISB website at *http://systemsbiology.org/*.

Another effort that goes hand in hand with ISB's systems biology approach is that of modeling a cell *in silico*. Instead of the traditional experiments done *in vivo* (in the body), or *in vitro* (in glass; a petri dish or test tube), *in silico* (in silicon) experiments are done in a computer. This ambitious effort may allow faster and cheaper development of drugs and a quicker understanding of how disease perturbs the body's systems. Because of limited knowledge of molecular dynamics and cell biology, as well as the enormous computing power required, today's efforts typically focus on models of cell behavior that center around the metabolic relationships of interest. However, as knowledge and computing power grow, these efforts may replace traditional techniques in medical research.

One medical technology in development for decades is finally entering medical practice: tissue regeneration. Dr. Anthony Atala of the Wake Forest Institute for Regenerative Medicine has grown nearly two dozen working body parts such as muscle, bone and a heart valve. A recent video on TED (Technology, Engineering, Design) highlights his work at *http://blog.ted.com/2011/03/07/printing-a-human-kidney-anthony-atala-on-ted-com/*. In it you will see Luke, now a healthy active college sophomore, but he was only 10 years old when Dr. Atala implanted a urinary bladder grown from Luke's own cells.

USING LIVERS FROM CADAVERS, HE AND HIS TEAM ARE LEARNING HOW TO GROW NEW ONES IDENTICAL TO THE PATIENT'S TISSUE.

Atala's research is wide-ranging and the technologies he's developing address an equally broad spectrum of needs. Using livers from cadavers, he and his team are learning how to grow new ones identical to the patient's tissue. To do this, the original cells are removed, leaving only a skeleton of the liver that includes the blood vessel tree. The patient's blood cells are perfused into the tree to regrow the vascular network, followed by the addition of the patient's liver cells. Dr. Atala's group is also working on a specialized scanner / printer that scans a patient's wound area and then 'prints' the various layers of the patient's cells directly onto the wound with a modified ink jet printer – like something from a science fiction movie.

They are also working on printing a kidney. Ninety percent of patients on transplant lists are waiting for a kidney. Because of the obesity epidemic the number of people developing diabetes and needing a new kidney is expected to grow. Dr. Atala's team uses a CT (X-ray) scan to image the patient's kidney layer by layer and sends the digitized information to a modified ink jet which prints the kidney. The entire process takes only seven hours. For now, the work is experimental, but it will eventually work its way into mainstream medicine.

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There are also several teams around the world that are trying to grow a human heart. Dr. Doris Taylor of the University of Minnesota reported on her team's progress at the American College of Cardiology in April of 2011. The team followed a process similar to what Dr. Atala uses with the liver. They acquired hearts from cadavers and added a detergent solution to remove the cells, leaving behind an extracellular matrix (ECM), or scaffold, consisting primarily of collagen. Adult stem cells from human patients were added and heart muscle began to grow on the scaffold. The heart normally begins beating within a week. Dr. Taylor has already accomplished this feat with rat hearts, but since human hearts to supply the ECM would not normally be available the team is investigating the use of pig hearts to obtain the extracellular matrix. There would be no transplant rejection because the heart cells are made from the patient's own stem cells, thereby side-stepping immune system rejection. A link to Dr. Taylor's work is *http://www.stemcell.umn.edu/faculty/Taylor_D/home.html.*

Dr. Stephen Badylak is deputy director of the McGowan Institute for Regenerative Medicine, a program of the University of Pittsburgh School of Medicine and UPMC Health System. When Dr. Badylak first developed his technique for regenerating human tissue in the mid-1980s he was reluctant to discuss it with clinicians because they simply didn't believe his results. In fact, the field of regenerative medicine did not even exist when he first published his results in 1989. Dr. Badylak had discovered that by using the extracellular matrix from pig tissue to stimulate the body he could regrow whatever type of tissue that had been damaged – whether muscle, skin or blood vessel. Information on that program and a bio of Dr. Badylak can be found at *http://www.mirm.pitt.edu/people/bios/Badylak1.asp.*

Studies to fully understand his discovery are ongoing, but it seems to work like this: an extracellular matrix (ECM) is obtained from pig intestines and administered to the wounded area as a powder or thin sheet. ECM is a kind of cellular glue that holds tissue together so the cells can do their work. It is composed of very large protein molecules such as laminin, collagen and fibronectin, and forms a scaffold for the tissue. The ECM from Dr. Badylak's powder or sheets eventually breaks down in the body and gets replaced. During this breakdown a group of peptides called crypteins are left behind. These peptides not only have potent antimicrobial effects, they are also very powerful signaling proteins and recruit swarms of stem cells to the area to recreate the needed tissue.

An article in the July 8, 2011 issue of *Discover* magazine illustrates how powerful this technology is. (See *http://discover.coverleaf.com/discovermagazine/20110708?sub_id=CFmdKrt5bHAUV#pg70)* Corporal Isaias Hernandez was the victim of a bomb blast in Iraq that ripped off 70 percent of his right thigh, exposing portions of it down to the bone. Doctors normally recommend amputation once a person has lost 40 percent or more of a muscle group.

Hernandez refused and instead underwent a painful surgery to replace some of the tissue with muscle from his back. The procedure didn't work well, and he was left with limited function and a lot of pain. After a long rehabilitation process, he saw a science documentary about regeneration that ultimately led him to Dr. Steven Wolf, who was also experimenting with ECM. The ensuing surgery was successful and Hernandez now has enough muscle mass in his right thigh to equal the strength of his good leg. Badylak currently is refining his technique in the hope of discovering how to regenerate an entire limb, much as salamanders do.

For decades the dogma within the scientific community has been that the diseases of old age are a result of the aging process; that is, of the body's reduced capacity to fend off disease. Delaying the aging process would allow people to live a longer, healthier life. It has recently been determined that rapamycin, a drug normally used in transplant recipients, can increase the life span of middle-aged mice by 28-38 percent. The equivalent achievement in humans would provide more extra years of life than curing cancer and heart disease combined. Independent studies using rapamycin were conducted at the University of Texas Health Science Center in San Antonio, the University of Michigan at Ann Arbor, and Jackson Hole Laboratory in Bar Harbor, Maine. The discovery was named in the Dec. 18, 2009 issue of *Science* magazine as the runner-up for research breakthrough of the year. Researchers said, "We believe this is the first convincing evidence that the aging process can be slowed and lifespan can be extended by a drug therapy starting at an advanced age." Rapamycin appears to partially shut down the same molecular pathway as caloric restriction, which has been repeatedly shown to extend life in species after species.

A second compound, reseveratrol (a substance found in grapes and red wine), may also delay the aging process. A previous article in *Actuary of the Future* detailed this research. See "Predicting the Future, Predicting Mortality" at *http://www.soa.org/library/newsletters/actuary-of-the-future/2008/november/afn-2008-iss25.pdf* for further information.

The *Living to 100 and Beyond* symposia (see *http://livingto100.soa.org/)* have dealt with the topic of aging both from a research / theoretical point of view and from an implications standpoint (Click on 'Monographs' to gain access to the articles presented at past symposia). Over the years it has featured many experts who have conveyed progress in medical and aging research as well as many participants who have presented papers detailing the societal and personal ramifications of increased life and health expectancy. "Plastic Omega" (*http://www.soa.org/library/monographs/life/living-to-100/2002/mono-2002-m-li-02-1-held.pdf*) reviews some of the research into the aging process. In addition, the book *Living to 100 and Beyond* by Tim Harris, who is co-chair of the symposium, does an excellent job of summarizing some of the issues raised by living longer.

The scientific literature and the popular press alike are filled with examples of technologies that seemed impossible only decades ago, but which will become commonplace in coming years. Some are already having an impact while others are farther over the horizon, but it is certain that the prospects for health and longevity in the 21st century will be much improved compared to previous eras. ☆