the Earth's ozone layer led to the development of alternative refrigerants that have smaller environmental impacts. The impact of the energy expended on refrigeration and the release of refrigerants themselves on the environment has led to innovations in refrigeration efficiency.

Outside of the cold chain, other technologies have led to discoveries in low temperature physics. In 1985 the American physicist Stephen Chu (1948–) used lasers to slow down atoms so that they could be studied more closely. Because the motion of atoms generates heat, this project took place at a temperature only 240-millionths of a degree over absolute zero. Later improvements brought the temperature of atoms down to a millionth of a degree above absolute zero.

SEE ALSO *Bose-Einstein Condensates; Mechanical Equivalent of Heat; Ozone Layer and Ozone Hole; Superconductivity; Superfluidity; Thermodynamics, Second Law of.*

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REGENERATIVE MEDICINE

The idea of regeneration has had a long history, leading back to the mythical story of Prometheus and his regenerating liver. Biological researchers have been intrigued by the fact that some organisms can regenerate whereas others cannot. The obvious questions pertain to why this is so and whether we can learn how the regenerative process works and discover how to engineer it.

The current enthusiasm for the field now known as *regenerative medicine* is largely due to the announcement in 1998 of the ability to culture and produce renewing lines of pluripotent stem cells. The dual capacities of these lines of stem cell, to self-renew and also to be differentiated to become any kind of cell, suggested possibilities for regenerative medical treatments and cures. If only we could use what we know about cell and tissue growth and differentiation to develop replacement structures and/or functions, then we could treat degenerative diseases. Public enthusiasm for stem cell research brought immediate attention to the new field of regenerative medicine, even before researchers had achieved significant results. Despite the fact that the term had been used before, most reports give the American biologist William A. Haseltine (1944–) credit for making the term regenerative medicine popular through his public lectures and interviews.

That the idea of regenerative medicine is tied to the advent of stem cell research is evident at the National Institutes of Health (NIH), where the 2006 report called *Regenerative Medicine* features Prometheus on the cover and reports exclusively on the latest work on stem cell research. Stem cell research created a world of imaginable possibilities.

STEM CELL PROMISE

In 1981 researchers announced the successful culture of mouse stem cell lines, but that work did not provoke much public interest (Evans and Kaufman 1981; Martin 1981). In contrast, in 1998, when the American developmental biologists James Thomson (1958–), at the University of Wisconsin, and John Gearhart, at Johns Hopkins University, announced that they had each cultured a line of human embryonic stem cells, the news attracted immediate public attention. The scientists made clear that these cell lines were human pluripotent embryonic stem cell lines, which means that they had the capacity to become any kind of human cell if cultured in the right way. That is, the collection of cells could be made to become heart muscle cells, or pancreatic islet cells that give rise to insulin, or nerve cells, and so on.

These cells, in turn, might help replace function that had been lost in diseased patients. A patient with degenerate nerve disease and lost function, such as Parkinson's or a spinal cord injury, might be able to recover that function if the researchers could culture nerve cells that might not be exactly like the originals but that could nonetheless substitute for them by serving the same purpose. A patient with a degenerative heart disease might have damaged or scarred heart muscle cells, and if researchers could culture stem cells to produce healthy functioning heart muscle cells, those might be made to function instead of the damaged ones. Again, they might not have exactly the same structure or be in the same

places, but they might fill in by substituting the function. Pancreatic islet cells, wherever they reside, could produce insulin; these new cells could deviate structurally from the originals even further as long as they delivered the insulin as needed.

The public saw the possibilities of this exciting research and also learned that harvesting embryonic stem cells requires killing the embryo they come from, because embryonic stem cells are found inside the blastocyst stage of the embryo. This raised ethical issues for some; others noted that many embryos are discarded every year in fertility clinics, and they did not see an ethical dilemma given the possibility of doing great good for many with degenerative diseases. The debates about the ethics and policy of human embryonic stem cell research have often drowned out the reports about what researchers have actually been learning about the science.

Researchers have made great progress in using stem cells to study developmental processes. In learning about how normal development works, they have also learned a great deal about how regeneration biology works. In fact, culturing stem cells and transplanting them to people with degenerative diseases does not work very well. But the stem cell science is informing the development of therapies in other much more promising ways.

UNDERLYING ASSUMPTIONS ABOUT REGENERATION

Regenerative medicine begins with a foundation in regenerative biology. There we find many underlying and sometimes competing assumptions that shape both the science itself and how we think we can use it. In 1901 the American zoologist, geneticist, and embryologist Thomas Hunt Morgan (1866–1945) published *Regeneration*, a book that summarized work to date and laid out the issues. He pointed out that the biggest question is what regenerating cells actually do when an organism is injured. Are the cells each transformed into different kinds of cells to replace the missing parts? Or do they stay differentiated and also give rise to new cells that then undergo a new differentiation into the missing types of cells (Morgan 1901)?

Morgan recognized that regeneration is a complex problem that required understanding cells, development, mechanics, chemistry, and how individuals respond to their complex environments. A decade later, he went on to focus on heredity and won a Nobel Prize in Physiology or Medicine for his work in genetics. Morgan never saw development and regeneration as simply determined by heredity. Yet many who followed him did make such an assumption, or carried out their research as if that were a reasonable assumption. Many geneticists assumed that cells inherit chromosomes that carry the hereditary "information" that guides them and tells them how to differentiate and what kinds of cells they should become. This model, and the eventual central dogma that the DNA of chromosomes leads to RNA that leads to defined proteins, has persisted and gained wide acceptance. The model also holds as a corollary that cells become increasingly differentiated, and once they become differentiated as some kind of cell or other, there is no going back. Differentiation works in only one direction, and it was this view that dominated biology for most of the twentieth century.

Yet stem cell research began to challenge that set of assumptions. This is especially true of the work led by the Japanese medical researcher Shinya Yamanaka (1962–) on induced pluripotent stem cells (iPSC), which made clear that a differentiated body cell, such as a skin cell, could be reprogrammed with different conditions and a few different genes to become a different kind of cell altogether (Takahashi and Yamanaka 2006; Takahashi et al. 2007). Indeed, a body cell can be reprogrammed to become a germ cell that can become a blastocyst and can, in turn, give rise to pluripotent stem cells.

Researchers have sought to understand what this might mean for regeneration. It appears that humans have more interesting possibilities for regeneration than did Prometheus, for whom it was the liver itself that had to regenerate new liver cells each night after the eagle pecked out his liver every day. Now we have the prospects for reprogramming other cells not connected with the liver initially to take the place of liver cells and do their job. Questions now include: How does this work? Will the new cells remain differentiated and keep doing their new jobs? What progress are we making in turning regenerative biology into regenerative medicine?

REGENERATIVE MEDICINE

Already by 1981 researchers including the American biologist Eugene Bell (1918–2007) had successfully engineered skin tissue in vitro and transplanted it to living animals to replace lost skin cells. The goal of being able to repair wounds by replacing either tissue itself or at least a replacement structure and function has stimulated interest for decades. Efforts at tissue engineering have expanded considerably with the capacities of stem cell technologies, and research with stem cells has contributed significantly, even though not in the ways initially imagined. Since then, researchers have used various types of scaffolding such as mesh or plastic structures to guide cells into desirable shapes and to bring together cells into tissues. The result is a kind of biological mesh with great potential, for example, in treating damaged bladders or other organs where replacement material makes it possible for the organ to work effectively again.

As of the beginning of 2014, a Google search for ''regenerative medicine'' yields over six million hits. The NIH has a Center for Regenerative Medicine, as do many universities, medical centers, and independent research laboratories. Collectively, they are attempting to tap what we know about cells to cause them to do what we want them to do, and to keep doing it after the cells have been moved from laboratory to life form.

With the laboratory production of human embryonic stem cells, which stimulated the public's excitement about the possibilities for regeneration, the American biotechnology companies Geron and Advanced Cell Technology (ACT) started the first clinical trials. As of 2014, ACT continues its study of retinal regeneration to treat macular degeneration, whereas Geron halted its trial for severe spinal cord injuries in 2011. Far more clinical trials are under way or planned using differentiated stem cell lines, from hematopoietic cells from bone marrow, spinal cord stem cells, and mesenchymal stem cells in particular. These cells are not pluripotent, because they can become only certain kinds of cells after differentiation, but if those are the results we seek, then the limitations do not matter. In fact, having already partly differentiated cells may be an advantage, with less risk of their become differentiated or redifferentiated in a problematic way.

The California Institute for Regenerative Medicine, funded by the state of California, has explored ways to mimic Huntington's disease and Parkinson's disease, which are neurodegenerative diseases. Research focuses on learning what might be possible with iPSC, produced by taking differentiated cells and reprogramming them with a genetic mix. Perhaps programming cells to become neural cells and ensuring that they remain differentiated that way can produce more cells available for transplant and therefore lead to better therapies. Although this technology has not yet moved into clinical trials, researchers are learning a great deal about the targeted diseases that will help with other possible treatments as well.

Because regenerative medicine is a rapidly moving field, it does not make sense to try to summarize the current work. Instead, interested readers should consult the website of the National Institutes of Health Center for Regenerative Medicine for reports on clinical trials and updates on advances in research.

SOCIAL QUESTIONS ABOUT REGENERATIVE ENGINEERING

Because much of the current research starts with stem cells, which are perceived to be ethically fraught even in cases where they do not come from embryos, the public has had concerns. It is important for researchers to be clear about the source of their cells. Embryonic stem cells raise concerns for some people but not others. So-called adult stem cells, which are taken from any stage after the embryonic stages (including fetuses, technically), do not raise the same ethical concerns. But they raise questions about how to carry out clinical trials in cases such as Huntington's or Parkinson's disease for which we do not have good animal models on which to test. More ''ethically neutral'' iPSC lines provide reprogrammed cells for use but raise practical questions about whether they are sufficiently like the normal cells to serve the role they are asked to serve.

Another source of stem cells is umbilical cord blood, which contains a rich mix of potentially useful cells. This blood is typically thrown away, but there have been efforts to pressure women giving birth to bank their cord blood. Affluent patients can afford to pay for the procedure and the banking charges that follow, but many others cannot. This has raised questions about the extent to which private cord blood banking should give way to public banks, perhaps with some cells reserved for private patients but sharing the materials. The potential uses remain largely hypothetical, but the costs and pressures on mothers is real.

Although it might seem reasonable for researchers to work to develop therapies from adult stem cells, and learning more is surely a good thing, there are concerns as well. Some researchers who focus on adult stem cells claim that their work is ethically preferable to work on embryonic stem cells and that it is even better biology. Such claims are surely true for some particular examples but not in general. One example is the lawsuit brought by the American bioengineer James Sherley and the American cellular physiologist Theresa Deisher against the United States government in *Sherley v. Sebelius*. These adult stem cell researchers sought to put a stop to federal funding of human embryonic stem cell research and made some headway as the case began working its way through the courts in 2009. In 2013 the US Supreme Court refused to consider an appeal in the case, which effectively ended the effort to shut down government support of human embryonic-stem-cell research. The case shows the depth of concern about this kind of research and the complex ways debates have played out.

Other research has sought to develop replacement organs, using scaffolding and cells to grow into tissues inside the body. Other efforts to build artificial organs start outside the body. Some efforts are exploring the use of gene therapies, or of nanoparticles, or the possible use of stem cells as transport systems to deliver new cells or drugs, or other replacement structures or functions inside the body.

SEE ALSO *Blood Compatibility, Transfusion, and Transplantation; HLA Antigens; Stem Cells, Embryonic; Stem Cells, iPS Cells; Transplantation.*

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REGULATION OF CHOLESTEROL AND FATTY ACID METABOLISM

Cholesterol was first discovered in 1769 by the French doctor and chemist Poulletier de la Salle (1719–1788), in gallstones and bile acids. It has now been established through centuries of research that cholesterol is an essential lipid (fat) for mammals, as it is the major component of plasma membranes of mammalian cells as well as the precursor for synthesis of steroid hormones and bile acids. Although cholesterol is crucial for our survival, overaccumulation of cholesterol in circulation is a predominant risk factor for development of atherosclerosis, the major cause of cardiovascular diseases. Thus, understanding the regulatory mechanism of cholesterol metabolism should help us to maintain a healthy balance of cholesterol in our body.

OVERVIEW OF CHOLESTEROL METABOLISM

Mammalian cells obtain cholesterol through two sources: synthesizing cholesterol from acetyl-coA through a series of reactions catalyzed by more than 20 enzymes, and acquiring cholesterol from blood. In 1929 the French biochemist Michel Macheboeuf (1900–1953) discovered that cholesterol is transported in blood as a complex with a class of proteins called lipoproteins. These lipoproteins were first successfully classified by the American John Gofman (1918–2007), a scientist who was trained both as a biochemist and as a physicist. His unique training allowed him to use the method of analytical ultracentrifugation to analyze lipoproteins (Steinberg 2004). His work in the 1950s at Lawrence Berkeley National Laboratory identified several classes of cholesterol-containing lipoproteins based on the difference in their size and density that are known today as very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). It has been established today that these lipoproteins play important roles in transporting lipids through circulation.

The liver exports cholesterol along with triglycerides (TGs) through secretion of VLDL particles, which are composed of a hydrophobic (water-repelling) core of TGs and cholesteryl esters surrounded by a surface coat containing phospholipids, free cholesterol, and several lipoproteins. These particles are synthesized in hepatocytes (liver cells) by attaching lipids to apolipoprotein B (apoB), a lipoprotein indispensible for production of VLDL. During circulation, TG in VLDL is hydrolyzed by lipases to release free fatty acids, which are absorbed by adipose tissue for storage and other peripheral tissues as a source of energy production. LDL particles, which are generated from VLDL following the hydrolysis of TG, are more enriched in cholesteryl ester. These particles are a major source of cholesterol in circulation for usage by peripheral tissues. In contrast to VLDL and LDL, HDL is involved in transportation of cholesterol from cells in peripheral tissues, particularly macrophages, back to livers. These particles contain apoA instead of apoB. In humans, cholesterol is transferred from HDL to LDL and VLDL by cholesteryl ester transfer protein. As a result, the amount of cholesterol associated with HDL is much less than that associated with LDL in humans.