DISCOVERIES IN MODERN SCIENCE

Exploration, Invention, Technology

VOLUME

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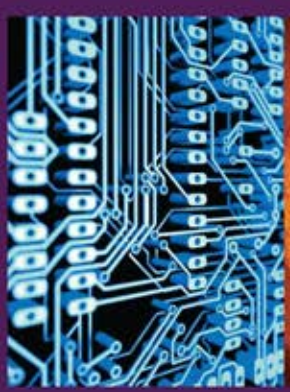


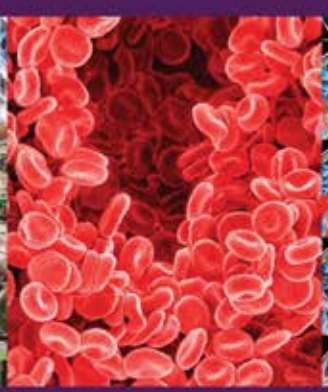
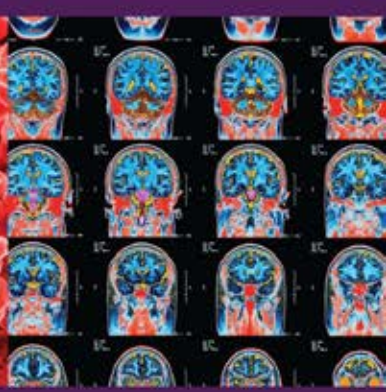

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James Trefil, Editor in Chief

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Planck-curve fitting and pioneering work in this field was carried out by the Potsdam astrophysicists Julius Wilsing and Johannes Scheiner.

Payne ignored the Plank curve and used a much more reliable quantum mechanical approach to atomic structure based on the ionization theory developed by Saha. By doing this, she showed how the strength of specific lines varied due to variations in the number of specific ions in each ionization state. She realized that spectral differences were due to variations in stellar physical conditions and not differences in chemical abundances, as had been previously suggested. At the heart of her thesis was the groundbreaking discovery that the starry universe was essentially chemically homogeneous. Payne found that common metals such as silicon, carbon, and iron were present in the solar surface material in about the same relative amounts as on Earth. However, another great breakthrough was the discovery that gases such as helium and hydrogen were vastly more abundant on the Sun than they were on Earth. Unlike many astronomers of the day, who believed that the solar composition was essentially similar to that of planet Earth, Payne had found that the starry universe was overwhelmingly made of hydrogen (a very satifying discovery because in 1920 Eddington had recognized that the conversion of hydrogen into helium was the main stellar energy generation process.)

Payne spent the whole of her professional academic life at Harvard University. In 1931 she became an American citizen and, in March 1934, she married the Russian-born American astrophysicist Sergei I Gaposchkin (1889–1984), who then came to work at Harvard, too. They lived in Lexington, Massachusetts, within easy commuting distance, and had three children, Edward, Katherine, and Peter. In 1956 Payne became a full professor (the first in Harvard's Faculty of Arts and Sciences) and she went on to be the first woman to head a Harvard University department.

SEE ALSO *Helium; Hertzsprung-Russell Diagram; Solar Atmosphere; Spectral Classification of Stars; Spectroscopy, Astronomical.*

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STEM CELL THERAPIES

SEE *Regenerative Medicine.*

STEM CELLS, EMBRYONIC

Two different kinds of things fall into the category called embryonic stem cells. The first consists of stem cells that occur in living embryos, those earliest stages of an organism's development before the form has become established. The second type of embryonic stem cell consists entirely in the laboratory, and includes stem cell lines that researchers have cultured after the pluripotent stem cells were removed from the inner cell mass of the blastocyst. Because of the culture medium and in vitro rather than in vivo conditions, this second type of cells behave in ways that we believe to be like stem cells within embryos, but we cannot know for sure.

Stem cells are like the stem of a plant. They have not yet differentiated into the distinct types of specialized cells that make up a fully formed organism. They have the capacity to become differentiated when the conditions are right, and they also have the capacity to divide and reproduce more stem cells like themselves. This dual ability to self-replicate and to differentiate characterizes all stem cells.

Aside from this defining dual ability, however, there is a taxonomy of different types of stem cells. Unipotent stem cells have the capacity to differentiate as one kind of cell only, so under normal conditions, a neuroblast stem cell can become only a neural cell. A multipotent stem cell can become either of two or more types of differentiated cells. A pluripotent stem cell has more options and can become any of the possible types of differentiated cells of the body. A

totipotent cell is not considered a stem cell, but has the capacity to develop into a whole organism rather than to differentiate into any particular kinds of cells.

EARLY RESEARCH

Historians have detailed a rich history of cell biologists' thinking about cells that have come to be called stem cells, but an important starting point for current research is grounded in the work of the American developmental biologist Leroy Stevens (see Maienschein 2014). Working at the Jackson Laboratory in Bar Harbor, Maine, Stevens was studying mice to test what causes cancers. In particular, since he was funded in part by tobacco companies, he asked about the role of tobacco, cigarette papers, and other factors in stimulating the development of cancers. Stevens discovered a strain of mouse, numbered 129, in which a high percentage of the males developed a kind of tumor called a teratoma, most often in the testes. Moreover, these tumors contained a mix of hair, teeth, and other kinds of cells that were obviously in the wrong place.

Stevens hypothesized that some of the cells that make up the inner cell mass of the blastula stage (which appears very early in the embryonic stage) had retained their pluripotent ability to become any kind of cell through later developmental stages. He tested the cells by grafting them to other mice, where they also produced teratomas. Labeling them pluripotent stem cells, Stevens noted that normally they should have gone on to differentiate in different places and at different times. (Lewis 2000; Stevens 1970).

ESTABLISHMENT OF STEM CELL LINES

This work caught the attention of others including the Austrian embryologist Karl Illmensee (1939–) and the American embryologist Beatrice Mintz (1921–), who together visited Stevens to learn more about these unusual mice. They borrowed some of the mice and demonstrated that the teratoma was, in effect, a disorganized embryo. That raised the possibility that some malignancies result not from mutations or other genetic changes, but rather because of difference in gene expression and development (Mintz and Illmensee 1975). Though that seems obvious today, in the 1970s it was surprising to think that development could have such profound determinative effects.

Soon thereafter, in 1981, the English developmental biologists Martin J. Evans (1941–) and Matthew H. Kaufman (1942–2013) in Cambridge, and also the American developmental biologist Gail Martin at the University of California San Francisco, succeeded in taking the pluripotent stem cells out of the blastomeres and cultured them. They thereby produced cell lines from pluripotent stem cells of the sort that Stevens had discovered. They started with the embryonic stem cells directly from the embryo—the first kind of embryonic stem cell that would normally go on to differentiate into any, and collectively into all, of the cells that make up a body. But they had also produced the second kind of embryonic stem cell, the one that exists only in a culture dish. They did not know whether it was exactly the same as the normal pluripotent stem cell, though it seemed to behave the same. As Martin said of this work, ''Given these results, it seems likely that there will soon be available pluripotent, embryo-derived cell lines with specific genetic alterations that should make possible a variety of new approaches to the study of early mammalian development'' (Martin 1981, p. 7638).

With this demonstration in 1981 that embryonic stem cells could be cultured and then manipulated experimentally came many questions, along with possibilities. To demonstrate that the cells in the cultured cell lines remained pluripotent, researchers established the standard that such cells must demonstrate their capacity both to self-renew and also to become differentiated as other kinds of cells. Obviously, it was not possible to demonstrate that any one cell could become any possible kind of cell. But testing the population of cells in the cell line with different culture media and different conditions should result in a diversity of different kinds of cells. If so, the cell line was designated as pluripotent.

Establishment of Human ES Lines. In 1997 we heard about the cloning of Dolly the sheep. When the news hit the next year that researchers had isolated and cultured lines of human stem cells, many people mixed up the two and thought that somehow human cloning had happened. What had happened was that the American developmental biologist James Thomson (1958–), a researcher at the University of Wisconsin, had cultured stem cells from human embryos. This required taking the inner cell mass from the blastocyst stage of the embryo, because that is the stage when the cells retain pluripotency. He wanted pluripotency in order to be able to culture the cells to become any kind of differentiated cells. In addition, since all the inner cell mass consists of embryonic stem cells, his team could harvest the whole batch of cells as a mass and culture them all without having to pick through other different kinds of cells first. And those cells came from blastocysts, which in humans can be in vitro (e.g., reside within a petri dish) up to that stage, after which they have to be implanted into a uterus in order to continue developing.

At the same time that Thomson announced his successful culturing of human embryonic stem cells, another American developmental biologist, John Gearhart at the Johns Hopkins University, published his work

on a human stem cell line that came from fetuses. (Technically, these were human embryonic stem cells in that they had the dual capacity of pluripotent cells to self renew and also to differentiate into any kind of cells. They did not technically come from embryos, but instead from fetuses, and therefore they were not ''embryonic stem cells'' in that sense. Today, such cell lines are considered technically ''adult'' rather than ''embryonic'' stem cells. Yet they were pluripotent: thus the need to be clear about definitions.)

Beyond Science: The Social Side of Stem Cells. The very term *stem cell research* evokes strong opinions, in part because of the way the story about human embryonic stem cell research appeared to the public. It did seem to tangle stem cells with cloning, and the stories made clear that getting at the embryonic stem cells inside a blastocyst requires killing the embryo. Researchers might talk about harvesting the cells or use other euphemistic language to try to disguise the fact, but given all that we know about embryos, getting at the inner cell mass of pluripotent embryonic stem cells requires taking them out. Taking them out requires rupturing the surrounding membrane. At that point, there isn't any embryo left; de facto, the researcher has had to end the life of, or kill, the embryo.

For those with a conviction that a human life begins with ''conception,'' which is taken to mean with fertilization, this embryo was a life. For many, such a life has special meaning. News that researchers were actually ending the life of some embryos, on purpose, in order to extract their stem cells raised serious concerns. Such research seemed to violate basic ethical constraints on killing. Yet researchers immediately pointed out that, in fact, they were carrying out such research only on embryos explicitly donated for the purpose or on embryos from fertility clinics that were going to be destroyed anyway.

Government Regulation. The fertility clinic business in the United States is not regulated federally, and there are no laws pertaining to the disposition of embryos. Some states have guidelines, and professional societies have established ethical guidelines for research. The National Institutes of Health (NIH) and the National Research Council (NRC) of the National Academy of Sciences (NAS) have both issued reports and recommendations. Nonetheless, the public debate around embryonic stem cell research did not depend on carefully argued positions or on facts, but resulted largely from an emotional response based on underlying assumptions and beliefs.

A series of US presidents have issued executive orders about human embryonic stem cell research, precisely because there is no legislation or clear set of regulatory guidelines at the federal level. President Clinton asked his bioethics advisory group for guidance and said that research should continue, funded with federal money through the NIH. President George W. Bush (1946–) consulted his advisors and said yes, research using federal funds could continue, but only on cell lines derived before he presented his views in 2001. He remained silent on whether he thought non-federal funds should be used, though he clearly felt that embryos should be respected in some ways, even if he was not sure exactly how. President Barack Obama (1961–) consulted his own bioethics advisory group and said yes, federally funded research should continue as long as it was done thoughtfully. Federal district court rulings and other debates have not changed this result: Human embryonic stem cell research is allowed in the United States, and it can be funded by NIH or other federal agencies, and there is no clear set of federally-legislated regulatory guidelines.

Other countries have taken a more regulatory role, legislating definitions and determinations that some research should be allowed and funded, while other research should not. The United Kingdom provides a set of standards allowing embryo research to the fourteenth day only, which allows embryonic stem cell research from blastocysts.

Controversy and Hype Surrounding Human Embryonic Stem Cell Research. Why all this fuss? Because people have deeply held convictions, on one hand holding that embryos are persons and deserve protection and on the other hand holding that embryonic stem cell research has great potential to help people based on research with embryos that were going to be discarded or would not have existed anyway.

This brings us to the promise of great therapeutic results from stem cell research. Early promises were clearly exaggerated, as they often are with scientific advances. Researchers see a way to attract funding and attention, and they are excited about what look like major innovations. They believe in what they are doing, and only a few recognize that they are exaggerating on purpose to make a point. In such a heavily contested area as stem cell research, they may become convinced that it is necessary to make the case more strongly to the public than they feel justified in doing among scientists, because they have to counter the extreme opposition of idealogues.

And so, with human embryonic stem cell research, a few biologists and medical researchers touted unproven claims for treatments and even cures for a range of horrible diseases. These scientists reasoned that if only we had enough research with pluripotent stem cells that come only from human embryos, then surely we could find cures for a range of diseases caused by degenerating or destroyed cells. Parkinson's disease, spinal cord injury, other neural and muscular degenerative conditions, heart

disease, juvenile diabetes, and so on: For each of these illnesses stem cells might be able to produce a cure by replacing cell function. This area of hope was termed regenerative medicine, because of the emphasis on regenerating lost function. With much at stake, different sides became polarized in their positions. In the midst of debate, we lost track of what was at issue. And we lost track of the fact that what was far more likely than magical therapies was that the research would teach us a great deal about development.

Lessons Learned. We have learned that development and differentiation is far more complex than we once thought. Cells do not just neatly become differentiated and stay that way forever. Under some conditions, they can be de-differentiated and re-differentiated as a different kind of cell. In addition, many epigenetic factors contribute alongside gene expression so that methylation and many other considerations that we are only beginning to understand play a role. Even when researchers can take those human embryonic stem cells, culture them, and get them to differentiate in what looks like just the right way, this does not mean that the new nerve or heart muscle or whatever will stay exactly that same way after it is transplanted to a new environment in the diseased body. It also does not guarantee that the cells will not become cancerous, or will not revert to a pluripotent stage and develop teratomas as Stevens's mouse strain 129 did, because the cells are in the wrong place at the wrong time.

As a result of such uncertainties, one line of research has proved very exciting. James Thomson and the Japanese medical researcher Shinya Yamanaka (1962–) independently developed ways to produce induced pluripotent stem cells that seem to be like the normal cells but started out as already differentiated body cells that were reprogrammed by adding a mix of genes (Takahashi et al. 2007; Thomson 2007). Called "ethically pure" pluripotent stem cells, the resulting cells did not require killing or discarding any embryos, yet they seem to have the same capacity. Yamanaka provided proof of principle with success in mice before his team and Thomson's both succeeded in humans as well (Takahashi and Yamanaka 2006). Research continues along these lines.

In addition, research continues on cancer stem cells. It seems clear that some kinds of stem cells are involved in some kinds of cancer, though whether these stem cells are related to embryonic stem cells or to more differentiated stem cells remains under examination. Embryonic stem cell research remains a vibrant and fast-moving field, full of surprises and discoveries.

SEE ALSO *Cell Division Molecular Dynamics; Cell Signaling; Dolly the Sheep; Regenerative Medicine; Stem Cells, iPS Cells.*

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STEM CELLS, iPS CELLS

The fountain of youth is an enduring story about the search for substances that can reverse aging. Some biologists believe that these substances may lie within the human embryo. As the embryo develops, molecules start to mature and age the cells of the organism, and biologists reason that they can manipulate these same