Stem Cell Technology and Other Innovative Therapies
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EMBRYONIC STEM CELLS – THEIR PLACE IN MEDICINE

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Some 'truths' are more central than others to the core concepts of all ideological systems. Current work on the earliest stages of mammalian development can be viewed as fundamental to our understanding of life or as a transient fashion. I will argue here that work on embryonic stem (ES) cells is part of the tradition of development biology established by 200 years of research. The argument will be extended to suggest that manipulating embryonic stages of cell development is central to progress in medicine and that ES cells uniquely provide access to these early events.

Galileo Galilei (1564-1642) mapped the movement of objects in the solar system, and by 1687 in his *Philosophiae naturalis principia mathematica* Isaac Newton (1643-1727) proposed that unseen forces accounted for their movements. Galileo and Newton made their own telescopes and the resulting insights became eternal truths. Two of Newton's contemporaries are important for our argument because they made lenses into microscopes. Anton von Leeuwenhoek (1632-1723) in Holland and Robert Hooke (1635-1703) in England used microscopes to suggest that organisms were composed of cellular subunits.

In Paris, the Boulevard Raspail named after Francois Vincent Raspail (1794-1878) leads away from the Blvd. St. Germain bisecting the 5th and 6th arrondissements. The plate naming the street describes Msr. Raspail as a chemist and a politician. In the history of science, Raspail played a political role in establishing public funding for Universities, a central feature of modern French culture. He is also known for his insight that all cells come from other cells (Omnis cellula e cellula – 1825). The subject that concerns us here is the relationship between cells. Msr. Raspail recognized the importance of this when he stated 'Give me an organic vesicle endowed with life and I will give you the whole of the organized world' (see *The Birth of the Cell*, Henry Harris, Yale University Press). This quote

shows that Raspail knew that understanding how one cell transforms into another is at the center of life.

The idea that all plants and animals are composed of cells became accepted between 1820 and 1840. The existence and functions of bacteria and yeast remained controversial until later in the 19th century when Louis Pasteur (1822-1895) is recognized the many contributions of these smaller cells. By 1900 the cellular history of many simple animals and plants was known. The marine biology laboratories at Naples and Woods Hole, Massachusetts were established in 1872 and 1888. The microscopic analysis of the early developmental stages in invertebrate marine animals was a major activity at these centers. T.H. Morgan (1866-1945), the founder of genetics, trained at Woods Hole. At the same time the cells of the brain were identified. The Spanish anatomist Ramon y Cajal (1852-1934) was amongst the most distinguished students of brain structure. These anatomists clearly understood they were reporting about the way the cells in living organisms behave in time and space.

Interest in the cellular development of animals continued in the decades from 1900-1950 with a growing focus on the more complex development of vertebrates. The name of Hans Spemann (1869-1941) may not be spoken in every home in Germany but his contributions to knowledge have been recognized in many ways. He received the Nobel prize with Hilda Mangold in 1935. The main street in the Max-Planck Instutute in Tubingen is named Spemanstrasse. Spemann and his colleagues showed that the basic body plan of vertebrates is established rapidly when the embryo contains only few cells suggesting that fundamental aspects of animal form are established at an early stage of development.

Spemann's work was focused on the embryos of birds and amphibia because they were easy to obtain and observe. The small numbers and inaccessibility of mammalian embryos makes them much more difficult to study. But by 1958, techniques were developed to place a mammalian embryo in a foster mother (McLaren A., Biggers, J.D., 'Successful development and birth of mice cultivated in vitro as early as early embryos', *Nature*, 182, pp. 877-8, 1958). In 1978, the first test-tube baby Louise Brown was born in England (Edwards, R.G., Steptoe, P.C., Purdy, J.M., 'Establishing full-term human pregnancies using cleaving embryos grown in vitro', *Br. J. Obstet. Gynaecol.*, 87, pp. 737-56, 1980). This process is named in vitro fertilization, because mature eggs are recovered from the genetic mother and fertilized with sperm in a dish. The fertilized egg is then matured for a few days and implanted in the mother who will carry the developing baby.

Scientists call the earliest stages where there are few cells an embryo and the word fetus is used to describe later stages of vertebrate development (http://www.wordiq.com/definition/Embryo). There are many stages to development, when the embryo implants into the uterus it is at a stage called the blastula. The blastula is a very simple structure containing few cells that will form the body surrounded by supporting cells that will form tissues like the placenta. So in the procedure of in vitro fertilization (IVF) only the very first steps of development occur outside the body.

Immediately after the blastula stage the mammalian embryo generates the basic body plan. This process is called gastrulation and is of great interest but it occurs hidden from analysis. Researchers interested in tumors of the ovaries and testes showed that these tumors contain many cell types that are all derived from a single cell type. A cell that has the potential to generate all the cells of the body was then obtained from the normal blastula of the mouse and it was shown that these cells could be grown in large numbers in the laboratory. Remarkably these cells can be introduced again into a blastula, the blastula implanted into a foster mother mouse and normal offspring are born containing cells derived from the cells grown in the lab (Beddington, R.S., Robertson, E.J., 'An assessment of the developmental potential of embryonic stem cells in the midgestation mouse embryo', *Development*, 105, pp. 733-7, 1989). These lab grown cells can generate complete mice and this has become part of a technique that generates mice carrying modified genes. The cultured cells are called embryonic stem cells and their use in the genetic manipulation of mice has become one of the most powerful techniques in modern medicine.

Although it was known that embryonic stem cells could give rise to all the cells of the body, at first few people directly studied the development of ES cells into other cell types. Scientists interested in the somatic stem cells that make specific tissues in the body were the first to show that these intermediate cells could be obtained from mouse embryonic stem cells in the laboratory. They developed ways to show that these lab generated cells showed appropriate functions expected in the blood, the brain and other tissues. Many brain diseases are caused by cell loss or degeneration. Parkinson's disease is in a large part caused by loss of midbrain neurons that use the neurotransmitter dopamine. In animals, grafted cells that make dopamine can restore functions of the lost neurons (Kim, J.H. *et al.*, 'Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease', *Nature*, 418, pp. 50-6, 2002). Cells derived from either the developing brain or from ES cells can restore function but the ES cells

have the distinct advantage that they can easily grow in the laboratory and still produce large numbers of the right type of neurons. At present, it is not possible to obtain large numbers of these neurons from any other source. When in the 1990s primate embryonic stem cells were obtained, it was easy to imagine using these cells as a source of specific human cells (Thomson, J.A. *et al.*, 'Embryonic stem cell lines derived from human blastocysts', *Science*, 282, pp. 1145-1147, 1998). Increasing evidence suggests that it will be possible to isolate large numbers of cells with specific functions of clinical interest from human ES cells.

There are several reasons for believing that interest in ES cells must continue to grow. First the point discussed above, that many cells of the body may have evolved to have limited growth and ES cells may be the only way to generate large numbers of these cells. Second, it will likely be clinically important to study the events of early human development that are replayed every time ES cells differentiate. Third, the long-term growth of ES cells will allow a new understanding of human genetics. The interest in human ES cells is clearly in a tradition of investigation of vertebrate development that has developed over two hundred years. Seen in historical context, the current interest in differentiating human ES cells is not a transient fad but a fundamental transition that brings together developmental biology and medicine. Just as the insights of Galileo and Newton still inform us, the continued use of human ES cells will likely be central to medical research for many decades. The perspective first stated by Raspail is now a reality.