

## "On the Permanent Life of Tissues outside of the Organism" (1912), by Alexis Carrel [1]

By: Jiang, Lijing Keywords: [Tissue culture](#) [2] [Stem cells](#) [3]

"On the Permanent Life of Tissues outside of the Organism" reports [Alexis Carrel](#) [5]'s 1912 experiments on the maintenance of tissue in culture media. At the time, Carrel was a French surgeon and biologist working at the [Rockefeller Institute](#) [6] in New York City. In his paper, Carrel reported that he had successfully maintained tissue cultures, which derived from connective tissues of developing chicks and other tissue sources, by serially culturing them. Among all the tissue cultures Carrel reported, one was maintained for more than two months, whereas previous efforts had only been able to keep tissues *in vitro* [7] for three to fifteen days. Carrel's experiments contributed to the development of long-term tissue culture techniques, which were useful in the study of [embryology](#) [8] and eventually became instrumental in stem cell research. Despite later evidence to the contrary, Carrel believed that as long as the tissue culture method was accurately applied, tissues kept outside of the organisms should be able to divide indefinitely and have permanent life.

Carrel sought to investigate under what conditions tissues can be sustained indefinitely *in vitro* [7]. He speculated that degeneration and death of tissue cultures was the result of preventable events, such as the accumulation of waste products or the depletion of nutrition in the medium. While he originally planned to design a device that could automatically provide nutrition and eliminate waste products through the circulation of fresh medium, this technology proved cumbersome and inferior to periodic manual replacement of medium. Instead, Carrel designed a more feasible method, a serial culturing technique to prolong the duration of tissue cultures. In his serial culturing technique, Carrel transferred fragments of original tissue cultures to newly made media, where they could resume growth.

In the 1912 experiments Carrel cultured multiple tissue types, including connective tissues of blood vessels, heart, skin, muscles, peritoneum, and spleen derived from [chick](#) [9] fetuses. Additionally, Carrel experimented with tissues from adult dogs, and [Rous sarcoma](#) [10], a type of [chick](#) [9] cancer. Carrel's tissue culture method generally followed the hanging drop tissue culture methods, adapted for tissue culture from bacteriology in 1907 by [Ross Granville Harrison](#) [11] at [Yale University](#) [12] in New Haven, Connecticut. In hanging drop cultures, cells grow from tissue fragments embedded in amphibian lymphatic clot and form cultures on a hollowed slide. To form his medium Carrel used a mixture of blood plasma and embryonic extract which he titled plasma, rather than the lymph employed by Harrison.

Carrel compared three methods for transferring tissue fragments from original cultures into newly prepared culture media. In the first, tissue fragments were washed at laboratory temperature in Ringer's solution, a commonly used isotonic solution for physiological experiments. In the second method, the washing step was at zero degrees celsius. The third method had a more elaborate design. Carrel and his technicians kept the tissues at what he called the temperature of the organism, then usually regarded as thirty-eight degrees celsius, and they let the tissues grow onto a tiny piece of silk so that the tissue fragment sitting on the delicate fibers of silk could be easily removed for washing and transfer.

With all three methods, dividing cells were expected to concentrically grow out of the old plasma clot into the new medium, with the cells in the center of the old plasma degenerating. Carrel did not evaluate the results of the third method in his paper. The first and second methods led to similar rates of growth in derived secondary cultures. New passages of tissue cultures were thus generated and maintained in this manner. The rates of growth in the newly formed tissue cultures were diverse and were influenced by many factors not easy to control, such as the composition of the medium, the exact process in which the plasma clot was cut, and the frequency of the subculturing.

The embryonic [chick](#) [9] heart tissue used by Carrel both grew and exhibited contractions. These contractions, which Carrel called pulsations, lasted for several days in plasma medium. In order to measure whether tissues in the secondary cultures still retained their physiological functions, Carrel observed the pulsations of cells in secondary [chick](#) [9] heart cultures and recorded their frequency. Carrel showed that although [chick](#) [9] heart tissues in degenerating cultures showed no sign of pulsation, when he transferred tissue fragments from degenerated cultures into new medium, newly grown cells resumed pulsations. Based on those observations, Carrel concluded that tissue *in vitro* [7] may retain normal function for extended periods of time. At the time Carrel was writing the paper on these experiments, he successfully maintained [chick](#) [9] heart tissue cultures for over three months.

Although many tissue cultures generated through these experiments died during the course of experimentation, Carrel claimed most died due to microbial contamination rather than internal failures of the tissues or culturing techniques. Because of the significantly prolonged durations of tissue cultures achieved through those experiments, Carrel was optimistic about sustaining cultures for longer periods of time. In the 1912 publication "On the Permanent Life of Tissues outside of the Organism," Carrel

hypothesized that the duration of tissue cultures could be lengthened indefinitely, and that tissues should intrinsically be able to maintain permanent life [in vitro](#)<sup>[7]</sup> under ideal culturing methods. Carrel further developed this line of research on [cell immortality](#)<sup>[13]</sup>, and his 1912 experiments provided both the material and technological basis for his [immortal chick](#)<sup>[9]</sup> heart tissue culture. This series of tissue cultures kept growing for thirty-four years in Carrel's laboratory, and was regarded by many as immortal.

The 1912 experiments published in "On the Permanent Life of Tissues outside of the Organism" by Carrel introduced the first set of methods for maintaining long-term tissue cultures and explored the [morphology](#)<sup>[14]</sup>, growth potential, and retained functionality of cultured tissues. However, due to still unknown peculiarities in the serial culturing of [chick](#)<sup>[9]</sup> heart tissues, the heart tissue grew for a period longer than a chick's normal life span. This led Carrel to false conclusions about the immortality of tissues [in vitro](#)<sup>[7]</sup>. The concept of immortality as an intrinsic property of cells, represented by the publicized "Immortal [chick](#)<sup>[9]</sup> heart tissue culture," became an assumption in the study of tissue culture for almost forty years, and was influential in both scientific and public domains. Its accuracy was not seriously questioned until 1961, when [Leonard Hayflick](#)<sup>[15]</sup>, based out of the [Wistar Institute of Anatomy and Biology](#)<sup>[16]</sup> in Philadelphia, Pennsylvania, definitively showed that normal cells have only limited proliferative capacity [in vitro](#)<sup>[7]</sup>.

## Sources

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'On the Permanent Life of Tissues outside of the Organism' reports Alexis Carrel's 1912 experiments on the maintenance of tissue in culture media. At the time, Carrel was a French surgeon and biologist working at the Rockefeller Institute in New York City. In his paper, Carrel reported that he had successfully maintained tissue cultures, which derived from connective tissues of developing chicks and other tissue sources, by serially culturing them. Among all the tissue cultures Carrel reported, one was maintained for more than two months, whereas previous efforts had only been able to keep tissues in vitro for three to fifteen days. Carrel's experiments contributed to the development of long-term tissue culture techniques, which were useful in the study of embryology and eventually became instrumental in stem cell research. Despite later evidence to the contrary, Carrel believed that as long as the tissue culture method was accurately applied, tissues kept outside of the organisms should be able to divide indefinitely and have permanent life.

### Subject

[Tissue culture](#)<sup>[19]</sup> [Carrel, Alexis, 1873-1944](#)<sup>[20]</sup> [Stem cells](#)<sup>[21]</sup> [Stem cells--Research](#)<sup>[22]</sup> [Embryology](#)<sup>[23]</sup> [Rockefeller Institute](#)<sup>[24]</sup> [Science experiments](#)<sup>[25]</sup> [Germ Cells](#)<sup>[26]</sup> [Tissue Culture Techniques](#)<sup>[27]</sup>

### Topic

[Experiments](#)<sup>[28]</sup>

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- [1] <https://embryo.asu.edu/pages/permanent-life-tissues-outside-organism-1912-alexis-carrel>
- [2] <https://embryo.asu.edu/keywords/tissue-culture>
- [3] <https://embryo.asu.edu/keywords/stem-cells>
- [4] <https://embryo.asu.edu/search?text=On%20the%20Permanent%20Life%20of%20Tissues%20outside%20of%20the%20Organism>
- [5] <https://embryo.asu.edu/search?text=Alexis%20Carrel>
- [6] <https://embryo.asu.edu/search?text=Rockefeller%20Institute>
- [7] <https://embryo.asu.edu/search?text=in%20vitro>
- [8] <https://embryo.asu.edu/search?text=embryology>
- [9] <https://embryo.asu.edu/search?text=chick>
- [10] <https://embryo.asu.edu/search?text=Rous%20sarcoma>
- [11] <https://embryo.asu.edu/search?text=Ross%20Granville%20Harrison>
- [12] <https://embryo.asu.edu/search?text=Yale%20University>
- [13] <https://embryo.asu.edu/search?text=cell%20immortality>
- [14] <https://embryo.asu.edu/search?text=morphology>
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- [27] <https://embryo.asu.edu/medical-subject-headings/tissue-culture-techniques>
- [28] <https://embryo.asu.edu/topics/experiments>
- [29] <https://embryo.asu.edu/formats/articles>