



The Rise of Synthetic Embryos

Surashmi M, Sowmika KV*, Veeresh Babu P

Gokaraju Rangaraju College of Pharmacy, Hyderabad, Telangana, India-500090.

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*Corresponding author:

Email : sowmika227@gmail.com

Phone : +91 - 9391434556

ABSTRACT

Synthetic embryos refer to the artificial creation of early-stage embryonic structures, typically using *in vitro* methods. Researchers aim to replicate the complex process of early embryonic development in order to better understand the underlying mechanisms and to develop new approaches for fertility treatments, regenerative medicine, and disease modelling. Synthetic embryos have been developed using various techniques, such as stem cell differentiation, 3D printing, and microfluidic systems. Despite the promising results, there are still significant scientific and ethical challenges that need to be addressed before the widespread application of synthetic embryos becomes a reality. This abstract provides an overview of the current state of the field and highlights the potential benefits and limitations of synthetic embryos.

INTRODUCTION

The field of synthetic embryos is a rapidly growing area of research that holds tremendous potential for advancing our understanding of embryonic development and improving human health. A synthetic embryo is an artificial structure that mimics the early stages of embryonic development, created using stem cells and the manipulation of these cells in a controlled laboratory environment. The goal of creating synthetic embryos is to study the process of embryonic development and to develop new techniques for regenerative medicine and reproductive biology.^[1]

The use of synthetic embryos in research has numerous benefits, including the ability to study the causes of developmental disorders, the development of new treatments for infertility, and the assessment of the effects of environmental toxins on embryonic development. Additionally, synthetic embryos provide a valuable tool for studying the mechanisms of embryonic development, enabling researchers to control the physical and chemical cues that influence embryonic development. In this article, we will explore the current state of the field of synthetic embryos, including the techniques used to create synthetic embryos, the benefits and limitations of this

technology, and the ethical and social issues associated with its use.^[2] We will also discuss the future direction of this field and the potential impact of synthetic embryos on human health and society.

DEFINITION

Embryos that are produced artificially do not undergo fertilisation. These embryos are also known as artificial embryos because they can be created without the use of egg or sperm cells. A synthetic embryo is laboratory created structure that mimics the characteristics of a biological embryo.^[3] It is typically made by assembling cells, such as stem cells, in a manner that mimics the process of embryonic development. The goal of creating synthetic embryos is to study early development, understand life sciences, studying mechanisms of embryonic development or testing new treatments for infertility.^[4]

Characteristics of Synthetic Embryos

1. Comprised of stem cells: Synthetic embryos are created using stem cells, which have the ability to differentiate into various cell types found in the developing embryo. Stem cells also used to develop mini brains, liver, kidneys and other organoids.
2. Controlled laboratory environment: Synthetic embryos

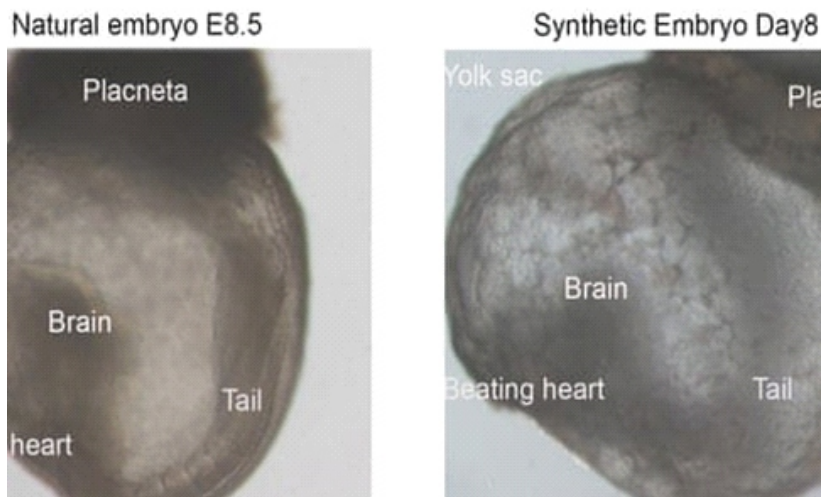


Fig. 1 : Differentiating between Natural and Synthetic Embryos

are developed in a controlled laboratory environment, where the physical and chemical cues that influence embryonic development can be carefully monitored and manipulated.

3. Mimics early stages of embryonic development: Synthetic embryos mimic the early stages of embryonic development, providing a valuable tool for studying the process of embryonic development.^[5]

4. Offers new avenues for research: The creation of synthetic embryos offers new avenues for research in areas such as the causes of developmental disorders, the development of new treatments for infertility, and the assessment of the effects of environmental toxins on embryonic development.

5. Raises ethical and social issues: While the creation of synthetic embryos holds tremendous potential for advancing our understanding of embryonic development and improving human health, it also raises ethical and social issues, such as the status of these artificial structures and the implications for the use of embryonic stem cells in research and therapy.^[6]

History

The study of synthetic embryos only really began in the early

twenty-first century. Scientists started experimenting with techniques to construct synthetic structures that resemble the earliest phases of embryonic development in the late 1990s and early 2000s.^[7] In the earliest experiments, small structures resembling blastocysts in the embryonic stage just before implantation in the uterus were made using a combination of cells and biomaterials.

Researchers made considerable strides towards creating more sophisticated artificial embryos with stem cells in the 2010s. Model embryos with a brain, a heart that beats, and the building blocks for all the other internal functions have been created from mouse stem cells by researchers at the University of Cambridge. This creates a new way to simulate the beginning of life. According to August 25, 2022, from the Journal Nature, Professor Magdalena Zernike-Goetz and her team used stem cells, which are the body's master cells and can differentiate into almost any type of cell, to build the embryo model rather than eggs or sperm.^[8] The scientists were able to mimic natural processes in the lab by guiding the three types of stem cells that are present in early mammalian development to the point where they start interacting. A particular collection of genes was made to express and interact in a particular way by the researchers.

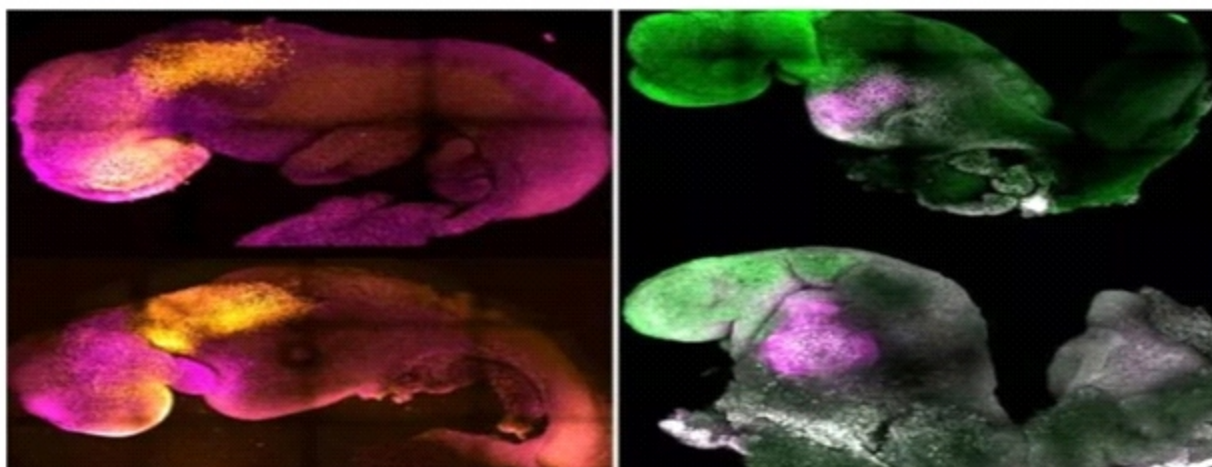


Fig. 2 : Brain & heart formation in natural and synthetic embryo

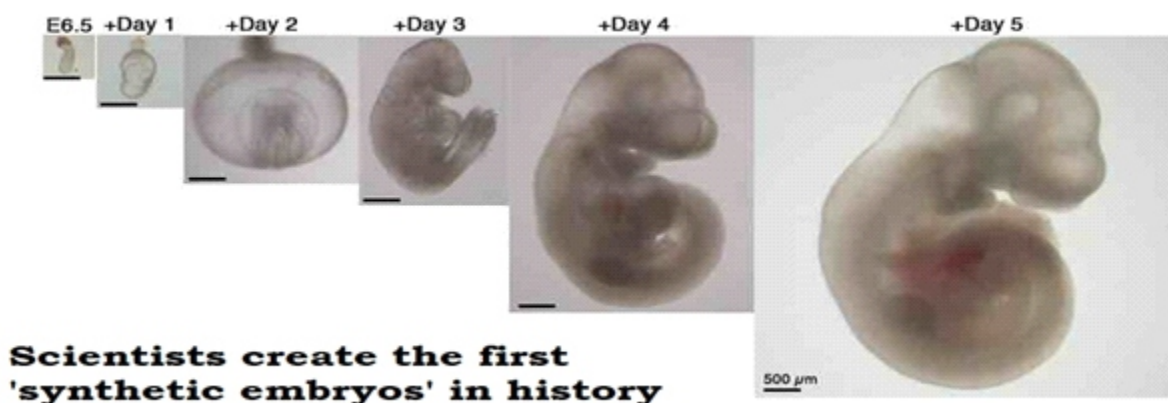


Fig. 3 : Developmental stages of synthetic embryo.

The researchers claim that their discoveries are the result of more than ten years of research that gradually created more complex embryo-like structures.

Research published in the journal *Nature*, might aid in explaining why some embryos fail to develop into healthy pregnancies while others succeed. The outcomes could also be utilised to direct the production and repair of artificial human organs for transplantation.

A critical initial step in the beginning of life is when an egg and sperm come into contact. It's a typical starting step in study on embryonic development as well.

By starting only with stem cells that had been nurtured in a petri dish, researchers at the Weizmann Institute of Science have created synthetic mouse embryo models outside of the womb. This shows that fertilised eggs are not used to raise them. This method brings up new study opportunities into how stem cells develop into various organs in the developing embryo.

Additionally, it may one day be able to create tissues and organs for transplantation using synthetic embryo model technology likewise, organogenesis.

Weizmann Institute researchers in Israel discovered that stem cells from mice could be induced to self-assemble into early embryo-like structures with a digestive system, the beginnings of a brain, and a beating heart, all without the use of sperm, eggs, or fertilisation.

The method used to create synthetic embryos was successfully created by stem cell researcher Jacob Hanna, who works at the Weizmann Institute of Science in Israel.^[9]

Process of Production

Production Method: Stem cells, which are cells that give rise to all other cells with distinct functions, are the basic units of the body. When stem cells divide effectively to produce additional cells in the body or a lab, daughter cells are produced.^[10]

These daughter cells can specialise into differentiated cells with a more focused function, such as bone, blood, brain, or heart muscle cells, or they can develop into new stem cells. No other cell in the body has the ability to generate several cell types on its own.

The several sources of stem cells include:

1. **Embryonic stem cells:** The age range of these embryonic stem cells is three to five days. An embryo at this stage is called a blastocyst and has about 150 cells.

These stem cells are pluripotent, which means they can divide to create additional stem cells or differentiate into any form of body cell (polo-RIP-uh-tunt).

2. **Adult stem cells,** little amount is present in the majority of adult tissues, such as bone marrow and fat.

Up until recently, scientists believed that adult stem cells could only produce other cells of the same kind.

3. **Adult cells that have undergone genetic reprogramming to mimic embryonic stem cells:** Common adult cells have been successfully reprogrammed to resemble stem cells. By altering their DNA, scientists can reprogramme adult cells to act like embryonic stem cells.

4. **Perinatal stem cells:** Scientists have discovered stem cells in both amniotic fluid and umbilical cord blood. These stem cells can develop into a variety of cell types.^[11]

The healthy development of a human embryo requires a "conversation" between the tissues that will create the embryo and the tissues that will connect the embryo to the mother. Within the first week after fertilisation, three separate stem cell types start to develop; one of these will eventually mature into body tissues, while the other two will support the development of the embryo. One of these extra embryonic stem cell types will eventually give rise to the placenta, which connects the foetus to the mother and provides oxygen and nutrition.^[12] The other will develop into the yolk sac, where the embryo develops and receives its early sustenance.

Many pregnancies occur when the three types of stem cells begin to convey mechanical and chemical signals. Only pluripotent or ESCs (embryonic stem cells) are among the three types of stem cells. They can grow into any type of bodily tissue, according to Zernicka Goetz. However, they need an additional two types of embryonic stem cells to accomplish this.^[13]

They can be instructed to develop into these two additional embryonic cell types.

As a result, three different beginning cell types are produced from a single ESC line. Researchers were able to learn more about

mammalian ZGA in 2012 when cells that corresponded to the genome activation stage of development were discovered in mouse embryonic stem cells.

Applications

Synthetic embryos, also known as *in vitro*-generated embryos, are a rapidly advancing area of research in reproductive biology and biotechnology. There are several potential applications of synthetic embryos, including:

1. Studying early development: Synthetic embryos can be used to study the early stages of embryonic development, including the formation of germ layers, organogenesis, and tissue formation. This can help to uncover the underlying mechanisms of normal embryonic development, as well as the causes of developmental disorders.

2. Improving infertility treatments: Artificial embryos could be used as a means to improve infertility treatments, such as *in vitro* fertilization (IVF). By using synthetic embryos, researchers can study the fertilization process and determine what factors are critical for successful implantation and development.

3. Modelling diseases: They can be used to model human diseases and study the effects of drugs and other treatments. This can help to identify potential therapies for a range of diseases, including birth defects and developmental disorders.^[14]

4. Conservation: *In vitro*-generated embryos can be used to preserve the genetic diversity of endangered species. This could help to conserve species that are at risk of extinction and maintain their genetic diversity for future generations.

5. Biomedical Research: To test safety and efficacy of new drugs or treatments for various diseases

6. Regenerative medicine: It is used to generate cells, tissues, organs for transplantation, with goal of repairing or replacing damaged or diseased body parts.^[15]

7. Reproductive medicine: Synthetic embryos could be used as an alternative to traditional *in vitro* fertilization [IVF] methods, potentially avoiding the ethical and moral concerns associated with use of donated eggs or embryos.

8. Developmental biology: They can be used to study early embryonic development and to investigate the factors that control cell differentiation and tissue formation.

9. Stem cell research: They are used to generate pluripotent stem cells, which have potential to develop into any of cell in body. This can be useful in regenerative medicine, drug discovery.^[16]

Drawbacks

1. However, the source of stem cells has generated significant ethical questions. It is abundantly present during the growing stages of embryonic cells, however in order to harvest these cells, an embryo must be obliterated before it can be placed into a female womb.

2. As a result, researchers have been successful in their search for a different approach to source them.^[17]

3. The study of artificial embryos is a relatively recent development. Despite the fact that they have a great deal of potential for advancement in a number of fields, including the study of early human development, infertility treatments, and disease models. Inadequate technological and scientific

knowledge is another problem. The development and behaviour of these organisms are still mostly unknown because synthetic embryo creation is still in its early phases. The possibility of unexpected outcomes that could seriously affect people's health and wellbeing, include the emergence of atypical or risky growth patterns.

4. Many pregnancies fail at the stage when three different stem cell types start communicating with one another mechanically and chemically, instructing the embryo on how to develop appropriately.

5. Zernicka-Goetz, a professor of biology and biological engineering at Caltech, stated that so many pregnancies fail around this time, before the majority of women are aware that they are pregnant.

6. "The period is the cornerstone for all other pregnancy-related events. Pregnancy will fail if something goes wrong". It is a difficult technological process that calls for a thorough comprehension of the molecular and cellular systems involved in early embryonic development, raising the possibility for. There is also a possibility of unexpected consequences, such as the emergence of atypical or risky growth patterns, which could have detrimental effects on people's health and wellbeing, for the use of synthetic embryos, which could result in possible abuse or misuse.^[18]

Ethical Concerns

- a. Nevertheless, it's crucial to understand that there are already rules and international standards for stem cell research that serve as a framework for policing this field of study.

- b. According to a regulation that has been in effect in Australia since 2002, research using human stem cell embryo models would be subject to licencing requirements.

The length of time that researchers can grow human embryo models is also limited by Australian legislation, unlike laws in other countries, and this limitation is something that some researchers would like to see rectified.

- c. According to some philosophers, creating artificial wombs is morally required to assist address the unequal distribution of parenting responsibilities. However, according to other academics, artificial wombs might jeopardise a woman's ability to legally end her pregnancy.

- d. The debate over whether it is morally wrong to use stem cells to make a synthetic embryo is already taking place in court cases.

- e. In particular, their prospective application in reproductive technologies, the production of artificial life, and the usage of human-like entities for academic and commercial objectives raise ethical and moral concerns about the use of synthetic embryos. Concerns have also been raised about the misuse of synthetic embryos in the creation of new technologies.^[19]

Source of stem cells and permission are two more significant legal issues. The stem cells from early embryos were employed to create synthetic mouse embryos. However, creating artificial embryos from pluripotent stem cells may be conceivable in the future. The worst case scenario is when a person provides skin cells to study on creating organs to treat disease, but these cells are utilised to create synthetic embryos without their knowledge or agreement. Synthetic embryo use raises ethical and moral

concerns, especially in light of their prospective use in reproductive technologies, the production of artificial life, and the use of beings that resemble humans.

f. Lack of regulation: The production and usage of synthetic embryos are currently unregulated, which raises questions regarding the possibility of unethical acts.

In the United States, there is no specific federal law regulating the use of synthetic embryos. The National Academy of Sciences has published guidelines for research involving human embryonic stem cells, but these do not specifically address synthetic embryos.

In the European Union, the use of synthetic embryos is governed by the European Convention on Human Rights and Biomedicine, which states that human embryos cannot be used for commercial purposes or subjected to certain kinds of experimentation. However, these regulations do not specifically address synthetic embryos.^[20]

Research regulations: In many countries, the use of synthetic embryos in research is regulated by national or international research ethics committees. These committees ensure that the research is conducted in accordance with ethical principles, and that the welfare of any living organisms involved in the research is protected.^[21]

Patent Law: In some jurisdictions, synthetic embryos may be eligible for patent protection.

Because of the complex and controversial nature of the issues surrounding synthetic embryos, it is likely that the development of specific legislation will be a slow and contentious process, involving input from a wide range of stakeholders, including scientists, ethicists, religious leaders, and members of the general public.

Overall, the regulation of synthetic embryos is a rapidly evolving area, and the specifics of the rules and acts will depend on the country and jurisdiction in question.^[22]

CONCLUSION

The field of synthetic embryos is a rapidly advancing area of research that holds a great deal of potential for improving our understanding of human development and for developing new treatments for infertility and other reproductive health issues. Despite this potential, the development of synthetic embryos raises important ethical questions, particularly with regards to the creation of embryos without the involvement of gametes and the use of these embryos for research purposes.

As the field of artificial embryos continues to evolve, it is important for researchers, policymakers, and the general public to engage in open and transparent dialogue about the potential benefits and risks associated with this technology. This includes a careful consideration of the ethical implications of creating synthetic embryos, as well as a thorough examination of the potential applications of this technology in the medical and scientific communities.

At the same time, it is important to recognize the limitations of our current understanding of synthetic embryos and to proceed with caution as we explore this exciting area of research. This may involve the development of guidelines for ethical research practices, the creation of independent oversight bodies to monitor the use of synthetic embryos, and a commitment to ongoing dialogue and collaboration among stakeholders.

In conclusion, the field of synthetic embryos holds great promise for advancing our understanding of human development and for developing new treatments for infertility and other reproductive health issues. However, it is critical that we approach this technology with caution, engage in open and transparent dialogue, and carefully consider the ethical implications of this work

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REFERENCES

1. kVeldhuis JH, de Boer J, Dolleman M. Synthetic Embryos: A Promising Tool for Studying Embryonic Development and Improving Human Health. *Stem cells Int.* 2021; 6074095.
2. Cotta-Ramusino C, Rivas R. Synthetic Embryos: A Review of Current Progress and Future Directions. *Front. Bioeng. Biotechnol.* 2020; 8: 507.
3. Martínez-Redondo P, Sánchez-Adam F, Platero-Luengo A, Villar B. Synthetic Embryos: From Basic Science to Biomedical Applications. *Front. Cell Dev. Biol.* 2020; 8: 579063.
4. Sun N, Chen Z, Yang X. Synthetic Embryos: A New Approach to Understanding Embryonic Development and Improving Human Health. *Front. Biosci.* 2020; 25: 1057-1074.
5. Wu X, Wang Y, Li X. Synthetic Embryos: A Tool for Studying Embryonic Development and Improving Human Health. *Front. Cell Dev. Biol.* 2020; 8: 562448.
6. Tristan Frum, Tayler Murphy M, Amy Ralston. HIPPO signaling resolves embryonic cell fate conflicts during establishment of pluripotency *in vivo*. *eLife* 2018; 7 DoI: 10.7554/eLife.42298.
7. Kasey Lau YC, Hernan Rubinstein, Carlos W. Gantner, Ron Hadas, Gianluca Amadei, Yonatan Stelzer, Magdalena Zernicka-Goetz. Mouse embryo model derived exclusively from embryonic stem cells undergoes neurulation and heart development. *Cell Stem Cell* 2022; DOI: 10.1016/j.stem.2022.08.013.
8. Gianluca Amadei, Charlotte Handford E, Chengxiang Qiu, Joachim De Jonghe, Hannah Greenfeld, Martin Tran, Beth Martin K, DongYuan Chen, Alejandro Aguilera-Castrejon, Jacob Hanna H, Michael Elowitz, Florian Hollfelder, Jay Shendure, David Glover M, Magdalena Zernicka Goetz. Synthetic embryos complete gastrulation to neurulation and organogenesis. *Nature* 2022; DOI: 10.1038/s41 586-022-05246-3.

9. Jasmin Taubenschmid-Stowers, Maria Rostovskaya, Fátima Santos, Sebastian Ljung, Ricard Argelaguët, Felix Krueger, Jennifer Nichols, Wolf Reik. 8C-like cells capture the human zygotic genome activation program *in vitro*. *Cell Stem Cell* 2022; DOI: 10.1016/j.stem.2022.01.014.
10. Hana Benchetrit, Mohammad Jaber, Valery Zayat, Shulamit Sebban, Avital Pushet, Kirill Makedonski, Zvi Zakheim, Ahmed Radwan, Noam Maoz, Rachel Lasry, Noa Renous, Michal Inbar, Oren Ram, Tommy Kaplan, Yosef Buganim. Direct Induction of the Three Pre-implantation Blastocyst Cell Types from Fibroblasts. *Cell Stem Cell* 2019; DOI: 10.1016/j.stem.2019.03.018
11. Gianluca Amadei *et al.* 'Synthetic embryos complete gastrulation to neurulation and organogenesis.' *Nature* 2022; DOI: 10.1038/s41586-022-05246-3.
12. "The Ethics of Synthetic Biology: A Review of the Literature" by the Nuffield Council on Bioethics and "Synthetic Biology: Scientific and Ethical Considerations" by the National Academies of Sciences, Engineering, and Medicine.
13. National Academy of Sciences. Guidelines for human embryonic stem cell research. National Academies Press. 2017
14. ten Berge, D. *et al.* Wnt signaling mediates self-organization and axis formation in embryoid bodies. *Cell Stem Cell* 2008; 3: 508518.
15. Xu, P.-F. *et al.* Construction of a mammalian embryo model from stem cells organized by a morphogen signalling centre. *Nat. Commun.* 2021; 12: 3277.
16. Veenvliet, J. *et al.* Mouse embryonic stem cells self-organize into trunk-like structures with neural tube and somites. *Science* 2020; 370: eaba4937.
17. Harrison SE, Sozen B, Christodoulou N, Kyprianou C, Zernicka-Goetz M. Assembly of embryonic and extra-embryonic stem cells to mimic embryogenesis *in vitro*. *Science* 2017; 356: eaal1810.
18. Girgin MU *et al.* Bioengineered embryoids mimic post-implantation development *in vitro*. *Nat. Commun.* 2021; 12: 5140.
19. Bao M *et al.* Stem cell-derived synthetic embryos self-assemble by exploiting cadherin codes and cortical tension. *Nat. Cell. Biol.* 2022; 24: 13411349.
20. Kaufman MH, Chang HH, Shaw JP. Craniofacial abnormalities in homozygous Small eye (*Sey/Sey*) embryos and newborn mice. *J. Anat.* 1995; 186: 607617.
21. Lawson KA, Hage WJ. Clonal analysis of the origin of primordial germ cells in the mouse. *Ciba Found. Symp.* 1994; 182: 6891.
22. Council of Europe. European convention on human rights and biomedicine. Council of Europe. 1997.



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