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# ARTIFICIAL HUMAN EMBRYOS

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## INTRODUCTION

Two separate scientific teams recently announced the creation of the most advanced artificial human embryos to date. The research appeared in two publications in June 2023 and comes on the back of several academic papers over the last decade that reveal accelerating advances in a controversial field.

Two key events in the late nineties served as forerunners to this work.

First was cloning, which showed it was possible to reprogram a differentiated (specialised) adult cell to initiate development as a single-celled entity (effectively a single-celled embryo - like a zygote), and in the case of many cloned species, produce a fully grown animal. While human embryo clones have been created, none have advanced beyond several days' development. Cloning showed how cells thought to be on a one-way path from less to more differentiated could, with the right biological tools, be sent back to the very start. In other words, cells were found to be much more fluid than once thought and open to being manipulated. A cell at the very start is termed totipotent; that is, with the power to produce a whole organism; or in effect constitute an organism in its own right.

Second was the isolation of human embryonic stem cells (hESCs) from a natural human embryo, causing its demise. Such an embryo at about 5-6 days is called a blastocyst, within which are the hESCs that will continue developing as the body of the embryo. These cells are termed *pluripotent*, having the power to form all tissues of the body, but not the complete organism. Once hESCs were isolated and grown, research using them expanded rapidly. Consequently, many governments permitted research using human embryos involving their destruction to develop populations of hESCs. Scientists also found that it was possible to create cells like hESCs directly from adult cells without using an embryo. These are termed induced pluripotent stem cells (iPSCs), which avoid the destruction of human embryos inherent in obtaining hESCs. It is important to note that once human embryos were legally available for research, many if not most were not used to derive hESCs, but rather to train technicians in IVF, develop genetic tests to de-select certain embryos, and improve IVF culture media.[1]

These two discoveries accomplished the groundwork that enabled the creation of artificial embryos.

This briefing will describe what has been done so far with artificial embryos, why the work was done, what it may mean, and what might be next.

## TERMINOLOGY

This paper will use the term *artificial embryo* to describe the variety of entities manufactured by scientists. The word artificial seems most appropriate given its meaning – 'made by people, often as a copy of something natural'.[2] The term *natural embryo* will be used when referring to an embryo resulting from the union of sperm and egg.

Other terms used in the literature for artificial embryos include blastoids[3] (after blastocyst), synthetic embryos[4], SHEEFs (synthetic human entities with embryo-like features)[5], embryo-like structures[6], blastocyst-like structures[7], and human embryo models.[8]

## WHY DO THIS WORK?

The main justification for creating artificial embryos appears to be to study the stage of human development beyond 7 days. 7 days is about the stage at which a natural embryo will implant in the uterine lining. What happens during implantation and beyond, specifically the next week, has been described as a 'black box' that cannot be studied by current methods. However, with artificial embryos (on the assumption that they are sufficiently like natural embryos) this stage could be studied and potentially have therapeutic application in finding the causes of early miscarriages and their treatment, studying genetic defects at an early stage, and improving methodologies in reproductive technology. Artificial embryos could also be used in toxicology studies to test for adverse effects on embryos.

More controversial would be future advances that enable further development ex utero including the generation of organs that could be used therapeutically.[9] It is unknown at this stage whether this is possible, but the field is moving so rapidly that such a result is looking more probable.

It is also important to acknowledge that motives for creating artificial embryos can be mixed, and some researchers may be driven in part by the desire to simply know what is possible, and how far existing limits can be stretched. Hubris and pride for being the first can also be a potent stimulus.

A comparison with past promises of controversial research on nascent human lives will be addressed later on.

## A BRIEF DESCRIPTION OF WORK TO DATE

In one of the studies already referred to in the introduction, headed by Zernicka-Goetz's group in the UK, modified hESCs were combined with unmodified ones and coaxed to develop up to the equivalent of 14 days.[10] This point in time is important, as it is the time limit permissible in law up to which natural embryos are permitted to be developed. The significance of this time limit will be revisited. The artificial embryos produced in this study look like natural embryos but are also clearly different. For example, they cannot implant as they are a 'post-implantation model'. However, because they were developed to a post-implantation-like stage does not preclude the possibility that they are enough like a natural embryo to do so, if such an experiment were to be conducted. The authors also note, 'these inducible human embryoids do not mimic stages beyond primitive streak formation, nor do they contain all cell types of the gastrulation-stage embryo'. The primitive streak appears at about day 14 and marks the start of gastrulation, which is the process of setting up three different cell lineages that go on to form the different cell types of the human body. Hence, these artificial embryos appear not to be able to develop further in ways parallel to a natural embryo.

In the other study by Hanna's group in Israel, hESCs were coaxed into 4 different cell lineages, which were then recombined and allowed to develop.[11] With a success rate of 1%, the resulting artificial embryos look almost identical to natural human embryos at 14 days. Again, the cells were developed past the natural point at which embryos implant making it technically impossible for implantation in the body of a woman to occur. But since there appears to be agreement that to do so would be unethical, no one really knows what might be possible.

These two studies have built upon other earlier ones using hESCs as well as iPSCs to create artificial embryos with varying degrees of success.[12, 13, 14]

But there are two additional key pieces of research in other species that may pave the way for what might be possible with humans.

The first of these, again by Hanna's group and also by Zernicka-Goetz's but using a mouse model, showed that artificial mouse embryos could be developed in vitro up to a stage where organs formed, including brain tissue and a beating heart, a stage of development equivalent to about 4 months in a human.[15, 16] This is evidence, in the mouse at least, that artificially created embryos can develop much further than anything so far attempted with humans. In their recent paper on artificial human embryos referred to above, Hanna's group makes it clear their work is an attempt to extend what they achieved with mice – 'here, we implement critical adaptations to extend these findings to humans'.[17]

The second involved the creation of artificial monkey embryos that were transferred to a female monkey and initiated a pregnancy.[18] The embryos died within 20 days but did show it was possible for an artificially created embryo to implant and continue development, albeit for only a short period of time – around the equivalent of 6 weeks human gestation.

## ARTIFICIAL EMBRYO STATUS

What is the status of artificial embryos? Are they human beings and should they be afforded protection as human persons? The answer to this question involves considerable uncertainty.

Nevertheless, one starting point is to consider what key characteristics natural embryos have and then see how artificial embryos compare. These characteristics of natural embryos are as follows: they are human and genetically and epigenetically[19] distinct (notwithstanding the special case of twinning); they self-organise and are therefore organisms in their own right; they follow a defined pathway of development that can best be described as a continuum towards maturity, from conception through birth and beyond.[20] As more is learnt about embryos, additional key characteristics may yet emerge.

Artificial embryos are also genetically and epigenetically human, and depending upon the techniques used, may be considered distinct or a hereditary combination of two or more genetic lineages - as in the mixing of cells from different genomes using hESCs mixed with iPSCs.

Many artificial human embryos are self-organising entities like natural human embryos. Their origin is unnatural in that they might be collections of cells treated to initiate self-organisation, but they nevertheless direct their own development from within once whatever it is that initiates development occurs. They can therefore reasonably be considered as organisms – although this may be a stretch for some of the earlier work where it is not always clear whether genuine self-organisation did actually occur rather than some degree of differentiation of separate cells but without proper organisation. Some, such as in Hanna's recent paper (albeit with a low success rate), self-organise to produce a blastocyst that looks almost identical to a natural human embryo of similar age.

Artificial human embryos begin following a trajectory that is a continuum towards later stages of development, like a natural embryo. However, depending on the techniques used, there may be variations that perhaps could be described as coding errors introduced by the technology used. In this regard, artificial embryos could be viewed as human embryos with fatal flaws in development. The fact that studies with both mice and monkeys resulted in considerably more advanced embryos shows that artificial animal embryos can be made that are more committed to a continuum of development than what has been achieved with humans. This may or may not mean something similar could be done with humans, but somewhat strengthens the notion that the limited

development of artificial human embryos is, like with animals, nevertheless a continuum of development, just not as advanced.

Another way of thinking about status is to compare artificial embryos with an existing means of embryo creation that also does not involve sperm and egg, namely cloning. It has now been firmly established that animal cloning results in birthed offspring that can grow to adulthood even though the success rates are poor. The first such animal was Dolly the sheep, cloned in 1996 from an adult cell from a donor sheep. Embryonic Dolly, created from a single activated cell without sperm and egg fulfilled the requirements of being a natural sheep embryo, but with some defects. It was genetically and epigenetically a sheep, but unlike most sheep, identical to one clonal parent. Embryonic Dolly was clearly a self-organising entity and therefore an organism directing its own development, and on a developmental continuum from nuclear transfer to adult sheep. Most cloned animal embryos don't survive to birth, but some do, perhaps those with less damage.

No one could reasonably argue that Dolly was not once a sheep embryo. Using unique and artificial means to create a sheep embryo cannot deny Dolly's status in early development as a sheep embryo. Similarly, cloned human embryos ought to be considered as embryos even though, as far as can be known, cloning to birth has not occurred with humans and may never, if the damage from nuclear transfer is too great, or there is a poorly understood barrier to further human development arising from nuclear transfer technology. Cloned human embryos might best be understood as human embryos damaged by their means of creation and therefore with little chance of further development. Similarly, artificial human embryos might be considered embryos damaged by their means of creation, and (at least now) with little chance of development beyond 14 days.

The benefit of the doubt about moral status should therefore be afforded to artificial embryos on the grounds of being *sufficiently* like natural embryos - at least those artificial embryos created by the most recent techniques, and possibly some of those from earlier studies too. Moreover, what has been clearly articulated by scientists doing this work is that the goal is to create an entity as close as possible to a natural human embryo. Otherwise, claims that artificial embryos are needed to study early human development are rendered meaningless.

> To realize the promise of SHEEFs as systems for analyzing human embryogenesis experimentally will require generating SHEEFs that are as close as they can be to non-synthetic [natural] embryos without triggering the restrictions that would apply to them.[21]

Therefore, those not concerned enough about how close artificial embryos are to natural ones now, will soon be forced to reconsider.

## THE APPEAL TO THERAPY - HAVEN'T WE BEEN HERE BEFORE?

It is worth considering past experience involving early human embryo manipulation in which it was claimed that new therapies would result and therefore the work had to be done. And on each occasion the community debate was intense. The justification for using human embryos like this has typically taken a utilitarian turn, including that the purpose for using them should contribute to their moral status.[22] In other words, it's not what the entity is that counts so much as what one wants to do with it. This is also reminiscent of the distinction made in the early days of cloning between so-called therapeutic cloning, which was deemed 'nice', and reproductive cloning, which was deemed 'nasty'.[23] In either case, cloned human embryos were the same entity, but put to different uses. It is not hard to see where these types of arguments might lead if applied to artificial embryos.[24]

What has been that past experience?

First, the use of human embryos to derive hESCs was claimed to be essential – 'It was the dawn of a new era. A holy grail.'[25] These cells could become any cell in the body and scientists would quickly figure out how to treat conditions such as diabetes, Parkinson's, Alzheimer's, and spinal cord injury, amongst others. Despite 25 years of research, not one treatment from hESCs has eventuated.[26]

Second, the combination of cloning and hESCs led to the claim that tailored cell types, and even organs, could be generated as an exact genetic match for sufferers of various conditions.[27] This was called therapeutic cloning and led to fierce public debate and eventually legal permission in many countries to proceed. Again, the dream has not eventuated, nor have cloned human embryos been reliably created, let alone led to tailored hESC lines. Moreover, this field of research will forever be remembered as one involving arguably the biggest scientific fraud of the modern era.[28]

Third, the creation of human/animal hybrids was deemed necessary to study early human development as well as to develop therapies.[29] Whereas human eggs were hard to obtain, animal eggs were not, and animal eggs were not associated with the plethora of ethical issues surrounding human eggs. Again, no new therapies or clinically significant applications have arisen from work with hybrids.

The point of raising these claims for potential therapeutic application from past embryo manipulation work is to highlight that such claims were overblown, possibly intentionally to gain public support and funding. And the same may be happening with artificial human embryos. Hence, claims about therapeutic applications coming from work creating artificial embryos should be treated very cautiously and not be allowed to derail proper consideration of the fundamental ethical issues.

## WHAT ARE THE IMPLICATIONS?

Strategies will continue to be developed to make artificial embryos that are as close as possible to natural embryos on a range of measures like appearance, developmental capacity, gene expression, etc. As artificial embryos become more and more like their natural counterparts, it is likely they will be increasingly used as an alternative to natural embryos in a laboratory setting. Research on natural embryos is constrained to some extent by whether parents in reproductive technology donate them to research, but also by the complexity of the regulatory processes. Natural embryos have parents whereas artificial embryos are far more loosely connected to the donors of the material from which they were made. If they can be produced in sufficient numbers they will most likely initially be used to study and refine techniques in reproductive technology, develop contraceptives and abortifacients, and test medicine safety (including potential toxins) on early human development.

Studies on embryonic development will expand and these will likely be used to indirectly push for an increase in the current 14-day limit, a limit that is almost universally applied.

The way this could possibly happen is along the following lines. As research on artificial embryos proceeds, they will be able to be grown beyond 14 days, and researchers will proceed because the 14-day limit does not currently apply to artificial embryos. Then work on say 28-day artificial embryos will come up against a series of obstacles because the artificial embryos are not 100% like natural embryos, perhaps more like embryos with developmental defects. This will then be used to argue that whatever work is current at the time is so promising, lawmakers should accept that artificial embryos probably are so close to natural ones that *de facto* work on them has already been happening for many years. Therefore, the 14-day limit should be dropped entirely and a new 28-day one applied to *both* artificial and natural embryos.

Variations to this type of argument could be framed.

In their 2018 paper on a possible 28-day rule, Appleby and Berendorf made the following statement.

> For several decades, the 14-day rule has been a shining example of how science policy and regulation can be developed with interdisciplinary consensus and applied across a number of countries to help fulfil an ethical and practical purpose: to facilitate efficient and ethical embryo research. However, advances in embryology and biomedical research have led to suggestions that the 14-day rule is no longer adequate.[30]

One of the bodies making such a suggestion is the *International Society for Stem Cell Research*, which recently changed its guidelines from endorsement of the 14-day rule to some form of loose oversight that might consider requests for increasing the limit on a case-by-case basis.[31]

The above statement by Appleby and Berendorf must be critiqued. The 'shining example' of the 14-day rule as they see it might instead be a shining example of an ethic driven by demand rather than by the ontological and moral status of nascent human life. Moreover, if the 14-day rule were to increase to say a 28-day rule, the point would be truly driven home that the 14-day rule was always arbitrary.

Furthermore, when researchers highlight the ethical challenges of working with 'real' human embryos, and at the same time manipulate biological material in an attempt to create those very same entities as an 'ethical' alternative, one wonders what kind of ethic is at work. Surely if researchers have ethical concerns about using natural human embryos in destructive experiments, they might also have ethical concerns about creating human life by unnatural means to likewise be subject to destructive experiments?

Gallagher argues on BBC News, 'The ambition for embryo models is to provide an ethical way of understanding the earliest moments of our lives.'[32] But for an embryo model to provide a way to 'understanding the earliest moments of our lives', the embryo model must be identical, or close to identical, to a natural embryo; and if the embryo model is an 'ethical way' as opposed to, presumably, the unethical alternative, namely using natural embryos, then using artificial embryos is also unethical. One can't have it both ways.

## A REVISED DEFINITION OF 'HUMAN EMBRYO'?

The definition of a human embryo was quite straightforward before cloning. It meant the entity arising from the union of egg and sperm up till eight weeks of development, thenceforth a fetus. Once cloning showed that an embryo could be produced by a different process, the definition changed. And now that artificial embryos are here, some are suggesting that the definition ought to be changed again.[33]

The current definition of human embryo in the UK's *Human Fertilisation and Embryology Act 2008* reads as follows: 'references to an embryo include an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo.'[34] This definition is expansive enough to include natural embryos as well as cloned ones, but clearly not artificial embryos as no egg is involved. Moreover, the definition is circular in that an embryo is an embryo if created by a 'process capable of resulting in an embryo'.

Rivron *et al.* argue that a new definition should be 'a group of human cells supported by elements fulfilling extraembryonic and uterine functions that, combined, have the potential to form a fetus.'[35]

The problem with such a definition is that no one knows whether such a potential exists since no artificial human embryos have ever been implanted in the body of a woman, which in any case everyone, at the moment, agrees should not happen. And there are no other criteria currently available to support potentiality. Rivron *et al.* therefore propose that the 'potential to form a fetus' should rely on certain 'tipping points' being achieved. These are: first, that the artificial embryo should have all the characteristics of a natural embryo developed in vitro up to a point decided by 'local ethical and regulatory considerations'; and second, that artificial embryos in animal models produce 'living and fertile animals in multiple species'.

Both tipping points set the bar very high.

The first tipping point opens the way to extend the 14-day rule at the behest of whoever pushes the regulators hardest. By referring to 'local ethical considerations' it also opens the way for an ethic of the least common denominator variety. If 'local ethical considerations' decide that a particular type of artificial embryo must have all the characteristics of a natural embryo at say 28 days to qualify as an embryo, then that's effectively a free-for-all with any artificial embryo that loses a single characteristic of a natural embryo just prior to that time.

The second tipping point would allow the creation, development, and use of artificial human embryos on an industrial scale right up to the point at which similar experiments with animals produce live-born and fertile offspring. Which may never happen.

The proposed definition would therefore permit extensive experimentation in creating and using artificial human embryos that might nevertheless soon be so much like natural ones that the difference would be hard if not impossible to determine.

## CONCLUSION

Researchers have made it clear that their goal is to create artificial embryos that are like natural ones so that they can be manipulated in a variety of ways justified by ill-defined therapeutic ends.

Some current artificial embryos are similar enough to natural ones to be given the benefit of the doubt and afforded the moral status of human beings.

Scientists have been permitted access to human embryos for experiments involving their destruction for decades, and also been allowed to produce cloned and hybrid embryos for research purposes. All without any advances in therapies, rendering claims for therapy from artificial embryos doubtful.

Advances in the treatment of infertility, miscarriage, and birth defects could advance significantly if the billions of dollars spent on all of this controversial research were redirected.

Scientists should abandon attempts to create artificial human embryos. To do so would show respect for human life at its very origin.

## ENDNOTES


1. See for example the licences approved by Australia's *National Health and Medical Research Council's* Embryo Research Licensing Committee. https://www.nhmrc.gov.au/research-policy/embryo-research-licensing/database-licences-issued Accessed 20 Oct 2023.
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