Over the past two years scientists from several institutions have isolated an embryo-like structure that behaves like an early embryo, but lacks several key cell types to develop into a fetus. These entities are alternatively called embryoids, gastruloids, asymmetric cysts, or SHEEFs (Synthetic Human Entities with Embryo-like Features). These structures self-organize, develop rapidly, and have what ethicists call “features of concern.” Should they come under the same regulations as embryos or are they unique entities?

For the purposes of this article, I will use the term “embryoids” because of their analogy to organoids. Organoids are not organs, just as embryoids are not exactly embryos. But organoids serve as cellular models of organs, and similarly researchers hope to use embryoids as models of early embryos. There are several groups working on embryo-like entities that they call “embryoids,” but not all of these embryoids are made the same way, and they do not all have the same features.

According to an MIT Technology Review article, two years ago a Michigan University team discovered that they had made embryo-like bodies. They found that these embryoids lacked key cell types to progress beyond a certain developmental point. However, these embryoids behaved enough like embryos that the team still destroyed them before the fourteen day limit.1

What exactly embryoids are, however, is a more difficult question to answer. The University of Michigan team made it very clear that these entities were not embryos, referring to them as “asymmetric cysts.” Their embryoids developed an amniotic sac and displayed self-organization, but they lacked key cells that would allow for development of the placenta, also referred to as the trophoblast. Additionally, the Michigan team only found one of the three cell types needed for embryonic development.2

Are Embryoids Just Another Type of Organoid?

Organoids are three-dimensional spherical structures that are typically grown on a scaffold and come from one of three sources: tissue, induced pluripotent stem cells (iPSCs), or embryonic stem
cells (ESCs). Importantly, their ability to form a three-dimensional structure is a key reason why scientists are interested in using organoids in research. Two-dimensional cell cultures do not display the same properties that three-dimensional ones do. As a result, if scientists want to accurately test whether a drug affects a certain organ in the body, they need to work with a three-dimensional model of those cell types. Organoids are also helpful in understanding how neighboring cells communicate with each other, something that has proven particularly helpful in cancer research.

Similarly, embryoids are also three-dimensional structures. While embryoids are typically made from embryonic stem cells that are placed in a gel matrix, they can also be made from induced pluripotent stem cells. The stem cells are placed in a constrained area, a microwell array for example, and allowed to grow, eventually forming an embryo-like ball. When the cells are not spatially constrained, they do not form embryoids.

Eventually these embryoids will exhibit a line of cells called a primitive streak that indicates body formation and directionality—that is, the development of a head and tail end as well as a front and back. In normal embryonic development, the embryo forms a primitive streak which then signals the cells to multiply and to migrate. This migration results in the formation of the three main cell layers (i.e., ectoderm, mesoderm, and endoderm). Some embryoids have shown evidence of a primitive streak and organization into three germ layers.3

Altered Nuclear Transfer

In 2004 William Hurlbut proposed altered nuclear transfer (ANT) as an ethical alternative to cloning.4 At the time, ANT was only a theoretical possibility, but research with embryoids has brought the theoretical to real life.

ANT involves making genetic changes to the nucleus of a cell before the nucleus is inserted into an enucleated egg (i.e., an egg from which the nucleus has previously been removed). The egg is then stimulated, causing the cells to multiply. The genetic changes that are made to the nucleus prior to insertion into the egg would prevent the egg from becoming a cloned embryo. According to Hurlbut, the entity would be akin to a biological artifact rather than an organism.

At the time that Hurlbut proposed ANT, one of the major criticisms from the scientific community was that the procedure was too cumbersome to make it practical. CRISPR-Cas9 had not been invented yet, but now the gene editing technology may make it feasible to make genetic changes to the DNA in a cell. Other critics say that this does not get around the ethical problems present with cloned embryos. The question is whether the product of ANT is truly a biological artifact or if it is a defective or seriously (and intentionally) disabled embryo.

Most embryoids show some organization into three-dimensional structures, but they do not exhibit global organization in the same sense that an organism does. From this perspective, embryoids are not, strictly speaking, the same thing as embryos even though they can serve as models for embryonic development.

Legal Considerations

In the United States and, until recently, around the world, research on human embryos is limited to the first fourteen days of development or the appearance of the primitive streak. The primitive streak is indicative of the first stages of the embryo developing a body plan.

When the fourteen-day rule was first determined by the National Research Council, the reasoning was that they did not want the embryo to experience pain or sentience, so they limited experimentation to a point that occurred before the formation of the nervous system or the brain. The Council determined that the formation of the primitive streak was a clear demarcation that occurred before the formation of the nervous system.

John Aach et al. argue in a 2017 eLife article that the fourteen-day rule is no longer adequate to draw the appropriate ethical lines because it was based on a linear track of normal embryonic development. As these synthetic entities (or SHEEFS as they call them) have demonstrated, they can bypass normal embryonic stages. They argue, instead, that ethical lines should be based on the emergence of the violation of the Dickey-Wicker amendment hinges, first, upon looking at origins of the embryoid (When is it derived?), and, secondly, upon whether or not embryoids are human organisms.
specific features of concern.7
Additionally the Dickey-Wicker amend-
ment—which has been included with
every appropriations bill since 1996—
prevents U.S. federal funds from being
used for the creation of a human embryo
for experimental purposes or for research
with human embryos in which they are
destroyed or discarded. The amendment
defines a human embryo as “any organ-
ism, not protected as a human subject
under 45 CFR 46 [the Human Subject
Protection regulations] . . . that is derived
by fertilization, parthenogenesis, clon-
ing, or any other means from one or more
human gametes or human diploid cells.”8

Pertinent to our present discussion,
the violation of the Dickey-Wicker
amendment hinges, first, upon looking
at origins of the embryoid (When is it
derived?), and, secondly, upon whether
or not embryoids are human organisms.

Ethical Questions

There are three areas of enquiry to high-
light the ethical issues surrounding
embryoids: 1) What are they? 2) How are
they made? and 3) What is their
intended use?

The embryoids considered in the MIT
article were made from embryonic stem
cells derived from an eight-day old
embryo. Because the extraction of an
embryonic stem cell leads to the destruc-
tion of an embryo, those who hold to the
sacredness of all human life from concep-
tion to death consider it unethical to cre-
ate human embryoids from such sources.

As noted earlier, however, embryoids also
can be made from induced pluripotent
stem cells, which are considered an eth-
ical source of stem cells. Despite being
considered an ethical source of stem cells,
the intended use of iPSCs remains a point
for ethical consideration. For example,
iPSCs have been used to make gametes,
egg, or sperm that can then be used to
create an embryo. Formation of gametes
in this manner, known as gametogenesis,
raises its own set of ethical concerns.

Embryoids seem to have many of the fea-
tures that define a biological organism.
They respond to environmental stim-
uli, exhibit self-organization, undergo
growth and development, and consume
energy. The cells within embryoids can
be said to reproduce in the same sense
that embryonic cells grow and divide.
However, the embryoid itself lacks the
necessary cells to grow into a human that,
in turn, can reproduce. Furthermore, its
self-organization is local in contrast to
the global and directional organization
of embryos.

Philosopher Melinda Fagan has pro-
posed that stem cells mediate the tran-
sition from cells to organisms. To com-
PLICATE matters further, embryoids and
organoids are both made from the stem
cells she claims mediate this transition.
Embryoids are more organized than organoids, making them closer
to an organism than an organoid; but
embryoids are still more simplistic in
structure and function than an embryo.9

Condic comments that

“...In the end, development has to be
defined by something other than
the molecular events that occur,
and I argue [in several papers] that the ‘something else’ is the capacity
to produce the first two cell types of
the embryo in an ordered develop-
mental sequence; i.e., the outcome
of an integrated developmental pro-
cess, not simply one or more mole-
cular events also observed during
the process of development.”99

If embryoids satisfy the definition of an
organism, then the follow-up should be,
“What kind of organism?” or as Condic
asks “Organized towards what?”

As noted earlier, John Aach et al. argue
that research with embryoids should be
limited, not by the fourteen-day rule, but
by the appearance of morally concerning
features. In this way, synthetic entities
that bypass any of the normal steps in
embryonic development can still be reg-
ulated based on the appearance of certain
features, such as the primitive streak.10

Embryonic development itself, however,
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