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17 What Is an 'Embryo' and How Do We Know?

Because of recent public excitement about cloning and embryonic stem cell research, more people than just developmental biologists are busily talking about embryos. Human embryos are central players in proposed legislation at state, federal, and international levels. But what is meant by an embryo? Rarely is the term defined or defined clearly. Yet the term is used in quite different ways and has evolved over time.

How have meanings changed, and for what reasons? What is the relationship between public and scientific understandings of embryos? Here, the focus is most directly on evolving understandings of the biological embryo, including recent shifting public meanings. In each case, both metaphysical and epistemological considerations are important. Yet only after the emergence of in vitro fertilization did the embryo become an object of significant ethical concern, and only with cloning and human embryonic stem stem cell research was it widely seen as an object of social concern. This essay considers the changing understandings of embryos.

Since at least 1771, with the appearance of the first edition of the *Encyclopedia Britannica*, the embryo has been seen as the earliest – and undifferentiated – stage of an individual organism's development. The embryonic stage was clearly separated from the fetal stage, with the first giving way to the second as form gradually emerged from unformed matter. Specifically, the 'embrio' was "in physiology, the first rudiments of an animal in the womb, before the several members are distinctly formed; after which period it is denominated a foetus. The 'foetus' denotes the child while it is contained in the mother's womb, but particularly after it is formed, til which time it is more properly called embrio" (*Encyclopedia*

Britannica 1771). In the eighteenth century, the change was taken as occurring at "quickening" or after, while today the shift from embryo to fetus is defined for humans as occurring at roughly eight weeks.

Clearly, the embryo has long been seen as unformed, as undifferentiated, and (following Aristotle) as having the potential to become an individual of the appropriate type but as not yet having been actualized as such. The *Oxford English Dictionary* offers a similar picture. Early usages of the term in the seventeenth century emphasized the 'Embryo' as "A thing in its rudimentary stage or first beginning; a germ; that which is still in idea as opposed to what has become actual in fact." It remains "in an undeveloped stage, 'that is to be'," presumably from the Latin 'Embryon' with a suggestion of "swelling within."

The past century of embryology textbooks has continued to provide similar interpretations, with emphasis on the coming into being and gradual emergence of form through the process called epigenesis. Even when embryology had begun to be called developmental biology, and even as the presumed efficacy of genetic inheritance began to overwhelm the previous presumed causal force of epigenetic emergence, the 1961 *Britannica* captured a typical understanding of the embryo. The 'Embryo' entry was written by Aute Richards, an emeritus University of Oklahoma zoologist who had been director of the School of Applied Biology and had written the widely used 1931 *Outline of Comparative Embryology*. He portrayed the embryo as beginning with the biological action of fertilization and existing through the process of cell division, through the cleavage of one fertilized egg cell into many. The early developmental processes occur with largely undifferentiated cells, and only gradually do they become separated histological types. Richards summarized that "it is not until these histological changes are accomplished that the young embryo is ready to function fully and to take an independent place in the world" (*Britannica* 1961, "Embryo") Of course, some species move from the embryonic form through a fetal or larval stage, but the earliest embryonic form of all species consists of undifferentiated cells and is unformed.

This was the epigenetic view that the embryo is the stage when form emerges gradually from the unformed matter, where 'unformed' means lacking in organic differentiation and without the body parts and systems that will arise later. Epigenesis was the dominant interpretation of the embryo into the twentieth century. The alternative was preformation, with form presumed to be already present from the beginning (see Maienschein 2003). To document the shifts in epigenetic and preformationist thinking, and to understand the changing patterns of debate, it is useful to focus on a sequence of six selected historical episodes. Underlying metaphysical questions about the nature of life, organisms, and parts provided one focus, while epistemological questions about how best to understand the emerging organism provided another. What was thought to be at issue shifted over time and in different contexts in ways that are instructive for our understanding of current debates about embryos.

HISTORICAL INTERPRETATIONS

Of course, there are many ways to divide up the millennia starting with Aristotle, but the following selected slices capture the range of shifting central issues. Each episode raises new questions and introduces new relevant factors, but each case also reveals instructive decisions about what is being studied, how to do the studying, and what relevant factors should be brought to bear in interpreting the results.

KEY PERIODS IN UNDERSTANDING EMBRYOS

The *Hypothetical Embryo* remained largely invisible and a matter for theoretical interpretation from Aristotle to the Enlightenment. Eighteenth-century debates laid out the traditions of preformationism and epigenesis that have continued.

The *Physical Embryo* of the midnineteenth to early twentieth century introduced comparative study of embryos in many species to describe the details of organismal change. When the work was done in the context of evolutionary theory it influenced the interpretations of developmental stages in important ways.

The *Biological Embryo* gained attention in the 1920s–30s, the embryological "golden age," with emphasis on the "organizer" and processes and causes of differentiation.

The *Inherited Embryo* of the 1950s–60s, with frog cloning and nuclear transfer, appeared with an enthusiasm for geneticism and eventually genomicism, and for reductionist methodologies.

The *Visible Human Embryo* started in the 1970s with in vitro fertilization (IVF) that took embryos out of the womb, with Nilsson's widely published photographs of fetuses that came (inaccurately) to represent embryos, and with use of other imaging techniques, all in the context of abortion politics.

The *Constructed Embryo* arrived with genetic recombination, cloning, and stem cell research that have allowed researchers to construct, deconstruct, and reconstruct embryos. Because of the fears and promises, the embryo becomes a public as well as a biological object.

We might also point to a seventh period, of the *Computed Embryo*, with an emphasis on collected data management and informatics, but that raises different issues and therefore will not be considered in further detail here.

The Hypothetical Embryo

The Hypothetical period, drawing more on theory and inference than on observation, provides important background about the interpretations that dominated thinking for more than two millennia. Aristotle outlined an epigenetic hypothesis for embryonic development that remained the only serious interpretation until the eighteenth century. According to Aristotle, embryo development was part of the natural processes of generation and corruption. Generation of animals, through sexual reproduction, involves combining fluids (or "semen") from both parents. This mingling of male and female fluids provides the material and the motive force for development.

More specifically, the female contributes the material cause that resides in the menstrual blood, and after "the discharge is over and most of it has passed off, then what remains begins to take shape as a fetus." This menstrual blood is not pure, however, and is simply "that out of which it generates." The material must be acted upon by the male fluid, which provides the formal cause and initiates the efficient cause for the development that follows. The formal and efficient causes therefore both act through the joining of the male and female fluids. Only then can the final cause serve as the telos for the living organism. Aristotle's four causes together bring about generation of each individual organism. "Thus things are alive in virtue of having in them a share of the male and of the female." The male and female serve as the "principles of generation" (Aristotle 1979, 99, 111, 133, 129).

Aristotle urged that the form must be guided by internal and not outside causes. "From the outset," an individual life requires a "soul" that guides the gradual unfolding of form (or epigenetic process) from the unformed matter. This soul – consisting of vegetative soul for all living beings, plus locomotory soul for all ambulatory beings capable of picking themselves up and moving around, plus rational soul for humans alone since only humans have the power to reason – gives the potential to become actualized as an individual organism.

Aristotle did not picture an embryo in our sense of a material cell that is fertilized by another cell to form a new union. Rather, his embryo was more process than object, and it was theoretical rather than observed for most species. He would have been able to see eggs only in such nonplacental animals as chickens, frogs, or insects. Yet what Aristotle did see, especially in chicks, looked initially unformed and only gradually actualizing the potential through the formation effected by epigenetic emergence.

As usual, Aristotle's interpretation was reasoned, accorded with available observable evidence, and provided an explanation for the manifest developmental processes of growth and differentiation. His epigenetic interpretation dominated into the eighteenth century and found resonance with leading Catholic thinkers. Saint Augustine held that the process of giving rise to a human life was gradual and that the human only becomes human after the fetus is formed and growing, after quickening. Abortion was considered a sin, but not homicide until after full "hominization" had occurred. An embryo was material and was alive, but it was not yet a human. For Saint Thomas Aquinas, the fetus first acquires a vegetative soul and begins to grow larger. Then later it acquires an animal soul and begins to become differentiated with all its animal parts. Only then does it acquire its intellectual or rational soul, and only then is it fully ensouled and human. This interpretation of "delayed hominization" dominated early Catholic history.

Epigenesis prevailed despite influences such as Pope Sixtus V, who issued the first papal declaration on the subject in 1588 apparently because of worry about rising prostitution in Rome. Sixtus decreed that contraception and abortion at any stage constituted homicide. Yet three years later when he died, Pope Gregory XIV pointed to the standard theological understanding that hominization occurs only gradually and returned to the long-standing interpretation that development is epigenetic and that the human emerges only later with full ensoulment. With time, additional observations, and additional philosophical reflection, however, other interpretations emerged from within natural philosophy to challenge Aristotle's epigenesis.

Some researchers were pushed toward an alternative because of their metaphysical materialism. If all that exists are matter along with the motion it experiences, then they asked how epigenetic development could yield form from nonform. Surely, such emergence requires some unacceptable vital force or directive, like Aristotle's hypothetical causes. The demand for materialistic metaphysic therefore led to preformationism. The form simply must be already in the very earliest moment of an individual's life. Otherwise, how could the necessary sorts of change occur (Roe 1981)?

This led to heated eighteenth-century arguments about whether an organism begins more or less literally preformed and just unfolds (or "evolves"), or whether it arises gradually and epigenetically through a process of embryonic development. While materialists emphasized the metaphysical unacceptability of hypothetical and apparently nonmaterial or vitalistic causes of emergence of form from nonform, however, epigenesists insisted on the primacy of an epistemology based on observation. And observation did not reveal tiny little already formed beings from the beginning. In important ways, this debate about the relative primacy of metaphysics or epistemology, about unfolding or emergence, about preformation or epigenesis, has informed all discussions since and even lies at the root of today's heated debates (see Pinto-Correia 1997).

The Physical Embryo

Debate began seriously in the late eighteenth and early nineteenth centuries, when embryos became Physical and visible in nonhuman species. Microscopes and an ethos of natural philosophy encouraged observation. The questions were, What could observations reveal, and what did the observations mean?

This debate played out, for example, in the work of Caspar Friedrich Wolff and Charles Bonnet, both looking at chick development. They looked at the same thing and even agreed about what it was that they saw, but their conclusions differed. Wolff was an epigenesist, for whom form emerges only gradually; Bonnet was a preformationist, who insisted that form must exist from the beginning of each individual organism. This is a story about competing metaphysical and epistemological convictions (Roe 1981, Maienschein 2003)

In 1759, Wolff studied the chick egg from fertilization through the twenty-eight-hour stage, which is shortly before the heart becomes clearly visible and begins to beat. As Wolff looked at chick after chick, hour after hour, he saw change, yes, but no chick. He did not see the chick form, a beating heart, or any small preformed chick. Instead, he witnessed movement and gradual change. He did consider that perhaps the form was just not visible yet because it was so tiny, but then stronger microscopes should reveal more detail and they did not. Wolff concluded that we should trust our observations. If we cannot see something, then we can legitimately assume that it is not there. This is a strong epistemological assumption about the nature of knowledge and justification, and it helped that Wolff's interpretation also conformed to the standard Arisotelian epigenetic interpretations.

Ten years later, Bonnet also understood the power of empirical observation. He also looked closely at many chicks, and he agreed that he did not see the formed chick before the twenty-eight-hour stage. He agreed with Wolff that they are not visible yet. But Bonnet concluded that the preformed form of the chick must be there, just somehow hidden in the egg. Since we know that form exists later, and it must arise through the actions of matter and motion, therefore it must be present at the beginning. Since vital forces were unacceptable to this materialist and since there was no other explanation for the gradual emergence of form, Bonnet concluded that the form had to exist already. If natural knowledge is to rely on observation, on logic, and on a proper materialistic metaphysics, then there could be no further question. An organism must be preformed in some way.

In retrospect, we see other alternatives. Bonnet might have said, as Newton did about gravity, "I do not know how form arises. Hypotheses non fingo." But Bonnet wanted an explanation of the origin of individual form and concluded that it must reside in preformation. The results were debates on several levels and the coexistence of competing interpretations of individual development with epigenesis and preformationism.

Further observations of embryos introduced new grounds for debate. So far, observers had seen chick, frog, and a variety of insect eggs, but it was not yet clear whether mammals also have eggs. Some assumed that all animals share the beginning as an egg. In 1827, Karl Ernst von Baer announced his discovery (in a friend's dog, killed for the purpose of experimental study) that even mammals have eggs, though it is difficult to observe their normal development since the eggs remain inside mothers. This led to enthusiastic study of the developmental stages of embryos in as many species as it was possible to study. Improved microscopes and microscopic techniques play a central role here as they made embryos in a growing number of species, and at increasingly earlier stages, more visible. Representations in illustrated plates and in wax models were important in presenting the embryo to other researchers and to the public (Hopwood 2002).

The last half of the nineteenth century was also dominated by the importance of the embryo for evolutionary theory. Darwin pointed to embryology as fundamental for interpreting relationships. In chapter 13 of the *Origin*, he asked:

> How, then, can we explain these several facts in embryology, namely the very general, but not universal difference in structure between the embryo and the adult; of parts in the same individual embryo, which ultimately become very unlike and serve for diverse purposes, being at this early period of growth alike; of embryos of different species within the same class, generally, but not universally, resembling each other; of the structure of the embryo not being closely related to its conditions of existence, except when the embryo becomes at any period of life active and has to provide for itself; of the embryo apparently having sometimes a higher organization than the mature animal, into which it is developed.

We know this was a rhetorical question, and sure enough he concluded, "I believe that all these facts can be explained, as follows, on the view of descent with modification." And that furthermore,

> the leading facts in embryology, which are second in importance to none in natural history, are explained on the principle of slight modifications not

appearing, in the many descendants from some one ancient progenitor, at a very period of the life of each, though perhaps caused at the earliest, and being inherited at a corresponding not early period. Embryology rises greatly in interest, when we thus look at the embryo as a picture, more or less obscured, of the common parent-form of each great class of animals.

In his *Generalle Morphologie der Organismen,* Ernst Haeckel went further. He saw "ontogeny as the brief and rapid recapitulation of phylogeny" and saw each individual's development as following the sequence of, and indeed being caused by, the evolutionary history of that individual organism's species. In his highly popular and widely translated books, Haeckel offered pictures of comparative embryology. "See," he seemed to suggest, "the human form emerges following the evolutionary development and adaptations of its ancestors." Form arises from form of the ancestors and unfolds following prescripted stages.

Darwin was not an embryologist; nor did he contribute directly to our understanding of the embryo. Nor did Haeckel. But while Darwin's use of the embryo in supporting evolutionary theory and in helping to interpret evolutionary relationships was consistent with various versions of either epigenetic or preformationist development, his view was decidedly preformationist. His was another preformationist interpretation based not on observations but on the metaphysical demands of his form of monistic materialism and motivated by his desire to provide evidence for evolution. This provided the context in which those studying cells and embryos worked at the end of the nineteenth century.

Only in 1869, that is, shortly after Darwin, did the Catholic Church alter its long-standing epigenetic interpretation, when Pope Pius IX decreed that hominization is immediate and begins implicitly at "conception." Unfortunately, his *Apostolicae Sedis* gives few clues about what led to his interpretation, which overthrew centuries of Aristotelian thinking, nor whether he was drawing on the recent biological discoveries of fertilization and of the mammalian egg.

Meanwhile, in Germany the anatomist Wilhelm His turned to human embryos. He collected every human embryo he could find and set up networks of physicians to contribute, seeking to establish the patterns of human development. The American anatomist

Franklin Paine Mall studied with His and carried human embryology to the United States. When His died, his collection went to Mall, then at the Johns Hopkins University. In 1914, Mall persuaded the Carnegie Institution of Washington to support his growing embryo collection, that led to the national Human Embryo Collection, which is still the most important source of human embryo material and history (Maienschein, Glitz, and Allen 2004).

His and Mall's embryos were all necessarily dead, since there was no way to study living human embryos inside the mothers. The embryos were seen as material objects, without questions about the appropriateness of collecting and studying them. Evidence that the public largely agreed includes the fact that the state of Maryland's Department of Public Health urged physicians to contribute. There were no known complaints about the project, perhaps in the belief that improved understanding of human embryonic development would have medical therapeutic value, over time.

The Biological Embryo

The 1920s–30s brought, as the Yale embryologist Ross Harrison put it, a "gold rush" of studies of causes and processes of differentiation. What causes the unformed to become formed: material mechanical changes within the embryo itself, as His had argued, or some set of special directive forces within or outside the embryo? Was there something unique about the living organism? Did we need what biologists by the twentieth century regarded as a metaphysically questionable vital force to explain emergence of form (and Hans Driesch did give up embryology and take up metaphysics precisely on this assumption), or is it something about the nature of the organic matter and its organization that allows development and differentiation of complex forms? How should embryos be studied?

Hans Spemann theorized that the tissue from the dorsal lip of the blastopore in amphibians has special powers to "induce" the rest of the embryo and to serve as a material "organizer" to produce differentiation and morphogenesis (Hamburger 1988, Maienschein 1991). Dozens of researchers took up the challenge to find the precise nature of the organizer. There is little evidence that this theory reached the general public or even biologists in other specialities often or in much detail, but an educated lay audience did ask whether such organization resulted from mechanistic or vitalistic forces. The physicist Erwin Schrödinger reached this wide audience when he asked, "What is Life?" and that discussion was clearly informed by embryo research.

The episode has an internal logic but also raises questions about our selective historical memory. This episode started with transplantation experiments of the 1890s and into the early twentieth century. These included the first stem cell experiments by Harrison with neuroblasts in tissue culture, and other experiments with nuclear transplantation. Today's stem cell researchers know little of this history of their own research, which leaves them – and the wider public – with the impression that something new and amazing (or horrifying) has been invented just in the last few years. Instead, stem cell and cloning research today is rooted firmly in traditions carrying back to Aristotle, through the work of the transplantation researchers of the late nineteenth and early twentieth centuries.

Harrison, Spemann, and their leading contemporaries assumed a metaphysical materialism. What exists are matter, its patterns of organization, and change over time. There is no room for vital forces or fluids, and they assumed that development is epigenetic. There is no form from the beginning, but it emerges gradually, over time, and guided by internal forces and factors. But how? That was the research program, focused on discovering the material processes that shape the embryo into an individual organized organism of the right sort. Epistemologically, they assumed that experimentation was the appropriate approach. Since it was not possible simply to observe natural processes and to see inside the egg and embryo, it was necessary to contrive experimental conditions. Manipulation of conditions, carefully controlling the environment as much as possible, could produce new knowledge. It was that new knowledge, taken collectively, that would reveal the patterns and processes of what came to be called morphogenesis, or the appearance of form.

The most important of the experiments were Harrison's on nerve fibers and Spemann's on the organizer. Both began with the idea that transplanting pieces of a developing embryo from one organism to another could reveal the relative contributions from the donor and the host. Working with frogs, which are abundant, have large eggs, and are easy to manipulate experimentally, they both saw the power of "heteroplastic grafting," or taking and recombining pieces from animals that look different – with different colors or sizes, for example. This made it easy to tell which tissue was from which organisms.

In 1907–10, Harrison refined the first tissue culture technique with neuroblast cells (essentially today's neural stem cells, known to give rise to nerve fibers). He "explanted" these cells, transplanting them out of a developing frog into a culture medium in a dish. They grew out as nerve fibers, apparently just as they would have done under normal conditions. This suggested that the cells contained an intrinsic capacity for differentiation, yet under normal conditions that differentiation would also be constrained and directed by the environmental conditions for each particular cell. The conclusion was clear: an embryo has internal capacities for development, and it also depends on cues and input from factors external to the egg and embryo itself.

Spemann focused on the earlier stages of development, on the stage when the blastocyst undergoes gastrulation. That is the first stage when the embryo begins to become visibly differentiated. The undifferentiated clump of cells undergoes rapid cell movement, with a flowing of cells into what is called the blastopore and the formation of germ layers. The clump becomes an organized ball of three layers that will become different parts of the organism. This is the first time when there is clear organization. Spemann asked, How does this happen? What causes the apparently undifferentiated mass of cells to become organized?

Perhaps, Spemann hypothesized, there is an "organizer." This must be material and it should be accessible through experimentation. Indeed, he found that the dorsal lip of the blastopore (that is, a particular set of a few cells at the still unorganized and undifferentiated blastocyst stage of development) induces organization of the cells. This particular material seemed to set up the layering of cells into the three layers. Other research suggested that the process is much more complicated, but during the 1920s and 1930s there was tremendous excitement about what seemed to be discoverable material causes of the production of form from the unformed cells.

Continuing research has reinforced this early conviction that it is the blastocyst stage of development, around days five to fourteen in humans, that is the beginning of organization and differentiation. This is the stage at which, in humans and other mammals, the preimplantation embryo must be implanted in the mother and must begin to exchange nutrients with the mother, or it will not survive. It is also the stage at which the embryo begins to grow, as it absorbs nutrients from the mother. And it is the stage when the clump of largely identical cells, now called embryonic stem cells, begin to undergo differentiation and development.

In addition to the biological scientific research, the social and cultural context began to have some influence. Harrison chaired the U.S. National Research Council (NRC), which promoted blood transfusions during World War I, and his tissue culture discovery inspired Rockefeller University's Alexis Carrel to expand tissue culture study for therapeutic applications. It is this research and the assumptions that underlie it that have provided the tradition of cell line development and application that have led to today's hopes for effective stem cell therapies. Harrison and Spemann were studying frogs, while Carrel and his medical colleagues worked with humans (Landecker 2004).

It seems likely that even if biologists had been able to study human embryos, the public response would have been positive. There is no evidence of early twentieth-century social concern about embryos. Human embryos were invisible, inside women. Because mammalian embryos remained hidden, early development remained a mystery to most people. The assumption was that human embryo development was similar to that of other animals, but even the experimental study of primate reproduction that began in the early twentieth century in places like the Carnegie Institution of Washington was slow to reveal insights about the earliest developmental stages (Maienschein, Glitz, and Allen 2004). Embryos must develop gradually, epigenetically, with form emerging through a process of stages. But how, and what directs the development? Is there really an "organizer," and if so what is it and how does it work? These questions remained.

The Inherited Embryo

The 1950s yielded one sort of answer with the Inherited embryo. The discovery of the structure of DNA, the stuff of heredity, has been well documented (Olby 1974, Judson 1979). Genetics had emerged as a field of study, and researchers had been exploring both the effects of the theoretical units called "genes" and the chromosomal structure presumed to contain the genes. Yet the study was largely abstract, and biologists such as Harrison did not see genetics as contributing anything to the study of development. As department chair at Yale, Harrison saw no point in hiring a geneticist, for example, since it was the study of organisms and their processes that he saw as the important work for biology.

Only in the 1950s did genetics begin to link effectively through molecular biology such that it was possible to imagine the DNA and its presumed genes as the concrete material basis for heredity. This, in turn, suggested that heredity provides the underlying causal shaping of developmental processes. Since every cell contains the same DNA and genes, and yet the cells begin to differentiate and to produce morphogenesis over time, it might be that the genes and DNA carry the necessary information to guide development. Genes could be the organizer that Spemann had sought.

In 1938 Spemann had suggested a "fantastical experiment" that would get at the relative contributions of the nucleus – with its chromosomes and genes – and cytoplasm. It was a conceptually simple transplantation experiment, removing the nucleus of one egg and replacing with another nucleus. He did not carry out this experiment, or not successfully, but in 1951 Robert Briggs and Thomas King did. They transferred frog nuclei to produce a new kind of hybrid. Cloned frogs graced the cover of popular magazines such as *Time* and *Newsweek*. John Gurdon went further in the 1960s, transplanting donor nuclei from frogs in later developmental stages into the eggs. He transplanted donor nuclei from an albino frog into the egg of a normally pigmented mother, and the offspring turning out to be like the donor nucleus, all albino. This suggested the very strong predominant influence of nuclear inheritance over development. Yes, epigenetic development might occur gradually, through time, as form emerges from the unformed material. But the guiding direction seemed increasingly to originate in the nucleus and the gradual expression of genetic information coded there. Accumulating evidence of this sort reinforced the idea that development is not only loosely directed but actually caused by the genes. And if so, then the information and determinants for development and differentiation are already present at fertilization. It seemed that development occurs by preformation after all, or at least by some version of genetic predetermination. To what extent is development actually determined or fixed, then, and to what extent can it respond to changing environmental conditions? Opinion shifted toward increasing determinism, reinforced by the enthusiasm for the Human Genome Project of the late 1980s and 1990s.

Public response to discussions of development during this time was limited, but what reaction there was remained largely curious rather than critical or concerned. The research might have raised new philosophical and biological questions about individuality and identity? After all, if an egg did not need its own nucleus, but another would do, what is the biological basis for concepts of self and other, of identity and autonomy? But this questioning seems not to have occurred to any significant extent. This research was largely taken as just that, biological research, to be carried out without much thought about its interpretations or implications.

The Visible Human Embryo

It has been only since 1978, when the human embryo became literally visible, that embryos have become an object of wide public interest. The birth of the first "test tube baby," the lively and normal little Louise Brown, first took human embryos out of the mother and into the public eye. Socially and culturally, we are still sorting out the implications of this discovery that the earliest human developmental stages can take place separately from the mother, and the questions raised about "what's in the dish." An embryo is still identified as beginning with the process of fertilization until, in humans and other mammals, the developing and differentiating organism gains all its organ systems and becomes a fetus. What happened after 1978 was initially not about changing scientific definitions of the embryo, though the emphasis shifted from animal studies to human embryo research for the first time. The primary changes right away were that the embryo gained individual meaning for prospective parents as well as public meaning, especially in the context of abortion politics.

Clearly, technology and images have been very important in introducing this scientific research to the public. Lennart Nilsson's photographs had provided a background of assumptions and interest. His stunning pictures were taken with a scanning electron microscope and endoscopes and showed the fetus in the womb.

The *Life* magazine presentation in 1969 gave most people their first images of the developing human. The fact that these were fetuses, and often later-stage fetuses, and the fact that these were highly colored and contrived pictures were not part of the public impression. Instead these images of little persons, sucking thumbs and looking innocent, became the public image of embryos. Many people, and perhaps a significant majority, still imagine embryos as these tiny clearly formed beings floating in the womb. This is not the biological embryo, but since it has become the public embryo for many people, any attempt to understand shifting meanings must take this misconception into account.

Another important social shift in meaning of the embryo comes with the recognized clinical importance of that clump of undifferentiated cells in a dish for patients. At significant personal cost in the United States and with significant personal investment in any case, those individuals engaging in IVF have come to see the embryo as the beginning of their baby. The biological fact that before implantation, this clump of cells is really just that, a clump of undifferentiated cells, does not take away the social and medical meaning invested in those cells.

Making the human embryo visible, with its potential for medical advantage, has produced increased funding, as well as increased public nervousness. Was IVF safe? For whom and under what conditions was it desirable, and who should pay for this in vitro process if it was considered a medical treatment? Countries have had different responses to embryo research. In the United States, IVF and embryo research generally has remained unregulated and largely privatized. What regulation exists is at the state level through laws and court case rulings, with overlapping and often contradictory results. The only federal restrictions are on funding through the appropriations bills for the National Institutes of Health. Canada, Australia, and the United Kingdom had different responses in 1978 and since, accepting IVF as a public good with public funding and public regulation. As a result, the human embryo is differently visible in each country.

The Constructed Embryo

In 1997, Ian Wilmut announced the first cloned mammal, Dolly the sheep (Wilmut 2000). As with Briggs and King's frogs, Dolly was produced by transplanting a donor nucleus into a host egg from which the nucleus had been removed. In this case, however, the donor nucleus came from an adult, and the result was seen as an "unnatural" hybrid that challenged assumptions about what is possible. Wilmut and his team brought experimental embryology to the public very dramatically and thereby first made the Constructed Embryo public though such research had already been long under way inside research laboratories. That Dolly existed, suddenly and surprisingly, as Louise Brown had existed suddenly and surprisingly out of IVF, challenged treasured assumptions within society as well as within science. Perhaps clones would develop differently than normal organisms, or perhaps they would have a diminished (or enhanced) life. What is normal and what is acceptable for embryos? the public began to ask.

Embryonic stem cell research, which reached public attention just a year later, raised new questions – both scientific and public – and generated prospects for regenerative medical therapies. But this research can (at least for now) best be carried out by harvesting undifferentiated embryonic stem cells from embryos. As we know from the heated debates, some members of the public find this unacceptable because they make the assumption that an embryo is already a person (or at least a potential person) and therefore we do not have the right to harm it.

This discussion gets right at the heart of what we mean by an embryo, and how we know. Scientists urge that we draw on scientific understanding of the embryo. A human embryo, especially before it is implanted in the mother, is really just a bunch of undifferentiated cells. To the best of available knowledge, no significant gene expression has begun; there is no differentiation; there is no significant growth. This is a bunch of cells dividing and dividing, at least up through the blastocyst stage. Only at that point, as Harrison and Spemann recognized, do differentiation and morphogenesis begin to occur. Only with implantation and gastrulation does the embryo begin acting and begin the epigenetic processes of development, informed by the heredity carried in the genes.

CONCLUSIONS

What, then, is an embryo? Some biologists prefer to call the preimplantation stages a "preembryo." Others urge that it would be easier and politically safer to drop the term 'embryo' altogether, though that is surely politically naïve. Who gets to decide what an embryo is? On the face of it, this is a biological question since embryos are biological objects. Therefore, biologists should at least have a say. They are quite clear on the matter. An embryo is not yet formed in the sense of structured with functioning differentiated parts, and a preimplantation embryo is really little more than a bunch of undifferentiated cells. A two-, four-, or even eight-celled preimplantation embryo can become twins, quadruplets, or even octuplets. Up through the eight-cell stage, the cells can even be pulled apart in the lab and the separated cells can develop individually. Or one or two or more cells can be removed (perhaps, as is commonly done now in fertility clinics, to test one of the cells genetically), and the rest can develop normally. This is clear. Biologically, an embryo is not yet formed, not yet differentiated, not yet recognizably human, and indeed not even unalterably an indivisible single individual.

Yet biologists do not alone "own" embryos. As public objects, embryos are much more complicated. A large political group would like to define embryos as beginning with fertilization, and as having status as embryonic human persons at that time. What we must realize is that in doing so, they are invoking metaphysical assumptions that lie outside science and that often depend on religious assumptions that are not shared by the larger community and cannot be justified on scientific or any other clear-cut grounds. Their epistemic warrant comes from such claims of "intuition" or divine knowledge or pure conjecture. Such meanings are, of course, highly problematic. We have yet to work through ways to deal with cases where the biological and social become so intertwined as in this case.

We need to ask what authority and what processes we have for carrying political and social decisions to restrict research back into the laboratory. Does the loboratory have any sort of protection, as some argue; is there a right to carry out scientific research? If so, when can there be limits and how are they to be imposed? The questions 'What is an embryo?' and 'How do we know?' remain works in progress – biologically, philosophically, and publicly.