Section I
Chapter 1

Human embryos

What is an embryo and how do we know?

Jane Maienschein and Jason Scott Robert

Introduction

Interpretation of what an embryo is has developed historically and in ways that are instructive both for bench science and for clinical translation. In particular, historical perspective illuminates changes in underlying assumptions. Similarly, interpretations of what counts as a 'healthy' embryo have evolved over time, reflected in and shaped by discussions of what is considered 'normal' for different purposes and contexts. Until recently, the concept of an embryo's being healthy was not part of discussions, though some interest had been expressed in what was medically normal or pathological. And for the most recent historical period, we have to ask 'healthy for what?' because embryos have come to have more than just reproductive meaning. For instance, embryos now have significance in both research and clinical contexts, as tissue potentially suitable for therapeutic purposes and not just for reproductive ends.

In this chapter, our approach is primarily historical, and we begin by focusing on scientific understanding of embryos, setting aside until the very end questions about ethics and other social contextual issues. We outline six historical periods of embryo research and understanding with their different sets of assumptions and goals, all of which inform our interpretations of the embryo today. Figure 1.1 depicts these six historical periods, which are not entirely distinct one from the next but nonetheless are characterized by key innovations in our understanding of embryos over time.

Gaining historical perspective matters because as we accumulate and compare periods across time, we can see how past assumptions have led researchers and the public astray (as, for example, with the claim that embryos cannot be dedifferentiated or the course of development reversed, or the suggestion that only embryonic stem cells have clinical value). We can also see how current assumptions may be misleading (for example, the assumption that the 'normal' or 'healthy' embryo has intrinsic integrity that must be preserved for moral reasons, which is problematic from a biological point of view). As well, we can show how our understanding of human embryos has been shaped by comparison with other animal embryos. This chapter therefore offers a brief introduction to all of embryo research, its contexts, and implications centred around organizing periods and ways of thinking.

Two caveats: first, we will usually refer to 'the embryo' generically as a category or kind of entity – that is, unless we add a modifier such as 'mouse' or 'human', in which case we are making a more limited claim. Second, the temporal referent of 'embryo' will vary from species to species. In humans, the embryo exists from fertilization until eight weeks, at which

The 'Healthy' Embryo: Social, Biomedical, Legal and Philosophical Perspectives, eds. J. Nisker, F. Baylis, I. Karpin, C. McLeod and R. Mykitiuk. Published by Cambridge University Press.

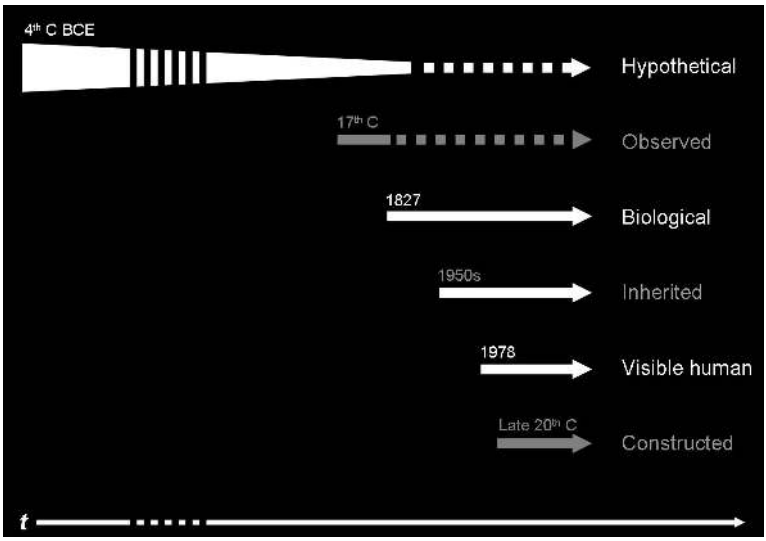

Fig. 1.1. Six historical periods in the history of embryo research.

point it is largely fully formed and referred to as a 'fetus'. Prior to implantation in the uterine wall, the embryo is sometimes referred to as the 'preimplantation embryo'. Several additional terms are used in some technical contexts to pick out particular stages of embryonic development (such as the 'zygote' and the 'morula'), but we will avoid such terms in this chapter.

Historical understandings of the embryo

The Hypothetical Embryo

The Hypothetical Embryo is brought to us by Aristotle and a millennium of Aristotelianism. If we can't see embryos directly, let's hypothesize about them. What could they be, given what we can see and what we believe to be the case? For more than a thousand years, Aristotelianism, as well as Catholic, Jewish and eventually Muslim law agreed: an embryo is the earliest developmental stage of becoming for an individual organism, before it has developed the appropriate form of what it will become. An embryo in this period was seen as emerging, not as already formed.

Aristotle did observe a few non-human embryos, notably in chicks, which were readily available at that time. Watching chick eggs develop provided strong empirical evidence in favour of the claim that at first there is no form and then there is. Form is visibly emergent, and in Aristotle's terms the physical appearance of form is guided by the working together of material, efficient, final and formal causes. That is, the formal cause is present with the coming together of material fluids from the mother and father, but the causes at first contribute potential that is actualized only over time and through the process of the causes working together. Development takes place through time and space, not all at once at a particular moment. An individual begins as a mixture of fluids, not in a flash of instantaneous conception, as later interpretations suggest (Vinci and Robert, 2005).

Despite the direct observation of chick embryos that only gradually come into being as material and then as formed chick embryos, Aristotle relied heavily on his hypotheses about

generation and coming into being. The same principles hold for all of generation, for Aristotle, and the interpretation is empirically supported but logically grounded. Aristotelianism fit with the popular and religious interpretations wherein quickening occurs gradually over time as the potential becomes actualized, and with early Catholic views that ensoulment occurs only later, apparently at 40 days after 'conception' (Bowler, 1971; Roe, 1981).

The Observed Embryo

A second historical period, ushered in by the Scientific Revolution, is characterized by a keen interest in the observation of embryos from many different species. Though human embryos would remain invisible, understanding them would not remain entirely hypothetical because those who were able to observe non-human embryos either assumed or inferred fundamental similarities (shared organic processes) across species. The goal of this period was to get at underlying principles and patterns of development through observation. This period witnessed the use of collection, comparison, and the extension of direct observation through microscopic techniques. A wide variety of studies, especially throughout western Europe, brought new interpretations of the embryo.

In 1771, the first edition of the *Encyclopedia Britannica* distinguished the Embrio (from *em* and *bryein*, for 'swelling inside') from the fetus. The embryo was 'the first rudiments of an animal in the womb, before the several members are distinctly formed; after which period it is denominated a foetus' (*Encyclopedia Britannica*, 1771). The distinction between embryo and fetus still holds today, as noted above, with the general understanding that in humans an embryo becomes a fetus at eight weeks post-fertilization, at which time the developing organism has assumed the basic human form with all the organ systems. When Leonardo da Vinci drew what unfortunately have often been called 'embryos', he was actually drawing very late-stage fetuses that were soon identified clearly as such. Leonardo's exquisitely careful sketches, though unpublished and largely unknown at the time, are evidence of the intense interest in the normally invisible embryo and later fetus growing inside the pregnant woman (O'Malley and Saunders, 1982, especially pp. 470–85).

The emphasis on observation and empiricism also came with changing background metaphysical assumptions about epigenesis and preformationism. Epigenesists hold that form emerges over developmental time, whereas preformationists hold that form is present from the beginning, and development is primarily growth. As historian Shirley Roe (Roe, 1981) has explained in detail, the traditionally Aristotelian epigenesist faced a challenge. If the form did not exist from the beginning but arose only gradually during the early stages of development, or during the 'swelling inside' the womb, then how did it do so? How could form come from the unformed? The only convincing explanation seemed to be the involvement of a driving formal cause, as Aristotle put it, or a vital principle of force, as epigenesists of the eighteenth century put it. These explanations required invoking a hypothetical, unobserved and apparently unobservable vital entity (see also Vinci and Robert, 2005).

For those embracing the new emphasis on materialism and mechanical causes, relying on such metaphysical inventions was unscientific and unsupportable. Materialists demanded a materialistic account of development, which seemed to require building the form in from the beginning. Presumably, they reasoned that the initial developmental stages of the embryo were preformed (or at least predetermined as to their form) and for this reason insisted that better microscopic techniques would reveal more details at earlier developmental stages. Epigenesists, on the other hand, continued to insist that ever more

refined microscopic techniques would confirm their view that the earliest stages are not formed. Along with debates about preformation and epigenesis, this period of the eighteenth and into the nineteenth century obviously brought intense interest in empirical study and in extending the range of direct observation.

The Biological Embryo

As a result of all that observation, the embryo began to be seen as a developing sequence of structured collections of interacting cells and parts. Researchers realized that it mattered tremendously how they studied the embryo, and therefore epistemological matters gained importance along with the ability to make different interpretations. Analysis of the parts and how they come to exist and work together came with the nineteenth-century period of the Biological Embryo, when experimental methods joined direct observation to offer expanded epistemological options. Researchers asked 'what's inside the embryo?' and 'how does it work?' Focusing on the processes and causes of biological function, the embryo was seen as a collection of cells that grows and differentiates, and takes on specialized functions in response to internal and external factors. There was a normal set of patterns and processes, and pathological alternatives. During this period, a keen interest developed in establishing 'normal' patterns and processes, with the idea of a normal sequence of stages of development.

This period can be said to have begun with Karl Ernst von Baer's 1827 discovery (in a dog) that mammals start as eggs and those eggs are cells, just as with chicks and frogs and other easily observed species. In the 1830s, he made careful observations of frog egg development and mapped out the changes. He drew what the process looked like, and in doing so mapped out an early version of what became known as a set of 'normal stages' against which any individual developing organism could be compared (Baer, 1834). By the end of the nineteenth century, it had become common practice to describe what were by then labelled as the normal stages of development for different species. This process brought assumptions both about what is 'normal' as distinct from abnormal and about the important 'stages' of development.

Of course, by the end of the nineteenth century, no set of normal developmental stages for humans had been determined because nothing could be seen directly and people had little to infer about the early stages. Nonetheless, by the beginning of the twentieth century, a good start had been made. In Germany, Wilhelm His was passionately interested in the mechanical causes of organismal development and in an effort to discover these causes, he sought to describe in detail the developmental steps and the sequence of changes. To study humans, he collected all the human 'embryos' he could find, working with physicians and morgues to do so. Of course, most of the early organisms available to him were fetuses rather than embryos. His work aimed to capture as much of the developmental process as possible and to work back as close to the beginning as possible (Hopwood, 2002).

Franklin Paine Mall visited His and took up his interest in human embryology. He brought this research focus to the United States, where he applied to the new Carnegie Institution of Washington for support for a human embryo collection. The funding he received established the spectacular Carnegie Embryo Collection. Under Mall, and with the help of the Maryland Department of Public Health which encouraged physicians to send material to Mall, the collection quickly grew to more than 10000 specimens housed at the Johns Hopkins University. When Franz Keibel moved from Germany to join Mall at Johns Hopkins, the effort expanded (Keibel and Mall, 1910). Although most of the collectors were keen to obtain early stage embryos, initially most of the specimens were fetuses

rather than embryos. The Carnegie Collection is now preserved at the National Museum of Health and Medicine of the Armed Forces Institute of Pathology in Washington, DC, but is soon to move to a new site in Maryland (O'Rahilly and Müller, 1987; Maienschein, Glitz and Allen, 2004; Noe, 2004).

In addition to collecting and observing human developmental stages, researchers took up experimental manipulation as a source of additional information and as a way of 'seeing inside' organisms. The conviction that experimentation opens up what is present and allows us to see aspects of normal development involves numerous epistemological assumptions. Yet by the beginning of the twentieth century, biologists and medical researchers accepted these assumptions. Better to gain additional information at the risk that it would require interpretation and might sometimes be erroneous than not to know at all – or so they assumed. For embryology, this experimentation meant an energetic exploration of diverse species with the goal of getting at fundamental principles and patterns.

Cell lineage provided a relatively simple approach to experimentation, leading to detailed descriptions about the differentiation that comes with each cell division. This research helped establish patterns of development for different species and suggested that some kinds of organisms, under some circumstances, are capable of remarkable flexibility. For example, despite injury to, or even destruction of, one cell at the two-cell stage of a sea urchin embryo, a fully formed larva could still develop, in a case of what was termed 'regulatory development'. In sharp contrast, other cell divisions seemed to produce differentiation that was not reversible and was highly determinate. Thus, the period of roughly 1890 into the 1920s brought lively discussion about the extent to which embryonic development was regulated or determined, and by what.

Another topic of interest was the role of fertilization. By the mid-nineteenth century, it seemed clear that a male and a female germ cell came together in a process called fertilization, which initiated development. Yet in 1899 at the Marine Biological Laboratory in Woods Hole, Massachusetts, Jacques Loeb used sea urchins to show that fertilization was not required to initiate cell division and differentiation. Changing the salt concentration in sea water could start the process. This finding raised questions about the nature of 'conception' and focused attention on the chemical and structural changes involved. In light of Loeb's work on parthenogenesis, as it was called, an embryo need not be the product of fertilization but could result from cell division (Pauly, 1987).

Work on regeneration added to the mix, and Thomas Hunt Morgan summarized that research in his 1901 book, *Regeneration*. At the heart of this line of study was the question of the extent to which an individual organism can replace parts and function after injury. Morgan saw regeneration as a window for understanding development and concluded that normal development is epigenetic rather than preformed or predetermined, with a good deal of plasticity in response to changing environmental conditions. Furthermore, this plasticity cannot be explained in terms of evolutionary adaptation (as August Weismann maintained) or hereditary determinism (as Wilhelm Roux suggested), but only as a response by the complex internal organism to changing environmental conditions (Morgan, 1901; Allen, 1978; Maienschein, 1991).

One especially active area of research was in transplantation experimentation. Because one of the central questions concerned the extent to which the early developmental stages were already differentiated (or formed) and the extent to which development could be shaped by the environment, experimenting offered great opportunity for increasing understanding. Frog eggs were particularly cooperative for experimental study. By the end

of the nineteenth century, Hans Spemann in Germany and Ross Granville Harrison in the United States were beginning to carry out a wide variety of transplantation experiments that began to yield intriguing insights into the patterns of morphogenetic development and differentiation. They transplanted parts by removing pieces (as in removing the area that gives rise to the ear, eye or limb), by adding pieces to foreign places (as in putting the part that would normally become an ear onto the back or belly), or by splicing together various bits in different ways. When researchers took pieces from differently pigmented species, they could watch whether a transplanted part developed as it normally would have in its natural environment or whether it adapted to the new environmental conditions.

Early experiments showed that development seemed clearly to involve a mix of determination by the intrinsic nature of the piece itself and its 'fate', along with an ability to respond in a more regulated way to a new environment. Clearly, development was epigenetic overall, but with some inherent characteristics that suggested not preformation, but a kind of determination. Understanding the patterns and causes of the balance was a prime focus for embryology in the first half of the twentieth century. This line of research also set the foundation for both cloning and stem cell research.

During this time, in a public lecture series in 1938, Spemann suggested that it would be exciting to carry out what he saw as an ultimate sort of transplantation, namely nuclear transplantation (Spemann, 1938). Because Theodor Boveri and others had shown clearly the importance of the cell nucleus in directing differentiation of the cell, Spemann saw nuclear transplantation as a wonderful way to test how far the nuclear impact would extend. He did not, however, carry out this cloning experiment. That task remained for Robert Briggs and Thomas King, who, in the 1950s, discovered that the nucleus does carry a great deal of determination with it (Briggs and King, 1952).

Another important line of transplantation research began with Harrison's experiments, first published in 1907. Harrison asked what would happen if he removed parts of a frog and cultured them in an artificial medium. He succeeded with the first tissue culture in 1907, and with more extensive results and discussion in 1910 (Harrison, 1910). Harrison's research showed that cells and tissue can develop outside the body and that the neuroblast cells he used can continue to divide and also become differentiated in response to the environmental conditions. Alexis Carrel took up this tissue culture work for applied medical purposes in the first half of the twentieth century; in later decades, others came back to these studies as the foundation for stem cell research (Landecker, 2007).

Clearly, by the middle of the twentieth century, researchers had collected tremendous amounts of data about how cells, tissues and parts respond to a variety of developmental conditions. Embryologists had laid out questions about the role of cells, cell–cell interactions, the efficacy of cell divisions and the emergence of structural patterns and accompanying functions. Embryologists realized that the nucleus was important, that chromosomes played a role in heredity and that Mendel's laws could account for patterns of inheritance. They did not, however, see inheritance as determining development or at least did not see how to connect the two.

The Inherited Embryo

By the second half of the twentieth century, the embryo was seen as inherited, in the sense of beginning with inherited material – first DNA, then genes, then the genome. Prior to this period, Mendelism had brought an early focus on inherited characteristics, with the Mendelian chromosome theory that the determining factors in heredity are the genes lined

up along chromosomes. Yet, as many embryologists pointed out at the time, because every cell had the same chromosomes, heredity did not explain what differentiates cells or what tells one cell to become a particular kind. Neither the discovery that chromosomes were made up of DNA, nor Watson and Crick's discovery of the structure of the DNA molecule addressed developmental causal questions.

In the 1960s, 'embryology' began to become 'developmental biology' and even 'developmental genetics'. Although researchers could not explain how the inherited genes translated into developmental differences, the underlying assumption was that the embryo was, at the least, highly constrained and possibly largely caused by inheritance – a highly predeterministic view.

This emphasis has had consequences for how the embryo is understood today. No longer 'just' an egg cell fertilized by a sperm cell that initiates processes of cell division and differentiation, the embryo became a complex of genetic inheritance and 'information' to be translated into functioning parts. The embryo could easily be seen as beginning at fertilization or 'conception', a view that reinforced religious interpretations that each individual person begins as conception. As we know, that view has ethical and legal consequences. It mattered tremendously that researchers embraced a view of the embryo as largely inherited rather than just *de novo*, and therefore the product of the previous generation. Though simplistic interpretations of that view are clearly just that – namely, simplistic – the public impression of the embryo has unfortunately been heavily influenced by this inherited genetically deterministic picture. It is noteworthy that this kind of picture persists today, despite both theory and data demonstrating its falsehood (Moore, 2002; Robert, 2004).

Recombinant DNA techniques developed in the mid-1970s helped to reinforce the public perception of embryos and life as highly genetically determined. As scientists brought their concerns about the safety of DNA manipulative techniques to public discussion, they created the impression that each individual life is highly genetically determined, that our individual genetic integrity was at risk. This view set the stage for further confusion in the late 1970s with the success of in vitro fertilization (IVF) in humans, drawing on agricultural successes with animal IVF.

The Visible Human Embryo

Swedish photographer Lennart Nilsson gave us widely circulated images of human fetuses in the womb which for many, many people came to stand for the human 'embryos' they could not picture and had never seen. Nilsson first photographed fetuses after death, capturing the various forms of this developmental stage and making human fetuses part of the public imagination. Later, in the 1960s, he began to photograph live fetuses during medical procedures using endoscopes. He reports that he waited long and not always patiently to capture the images he wanted, including one of a fetus appearing to suck its thumb.[1] These images appeared on the cover of *Life* magazine, in the pages, and eventually in many popular books. They have contributed significantly to public imagination of what an embryo is – even though they do not picture embryos at all, but fetuses.[2]

[1] See, for example, an interview with Nilsson at http://www.pbs.org/wgbh/nova/odyssey/nilsson.html (last accessed 7 July 2008).

[2] When the cloning of Dolly the sheep and then culturing of human embryonic stem cell lines were reported and the term 'embryo' appeared on front pages of newspapers and was uttered in local television news stories, many people imagined Nilsson's fetuses instead of the early unformed bunches of cells in the laboratory dish.

For the first time, IVF brought the human embryo out of the woman and into a glass dish in the laboratory, or more accurately in the clinic. IVF made the human embryo visible. At least the earliest stages were made to be visible – up to the time of implantation. After Louise Brown was born in 1978 as a result of IVF, and other successful IVF births following soon after, it became clear that researchers had learned to 'make human embryos'. Here for the first time, serious consideration of what might be meant by a 'healthy embryo' entered the discussion. It mattered that the human embryo in the dish be itself 'healthy' – one that, when transferred to a woman's uterus, would have the capacity to implant and contribute to normal and healthy development into a fetus and then a baby. Nobody wanted to produce 'defective' children, nor did anybody want to go through the expense and difficulties of IVF for less than a healthy birth. Healthiness of the embryo suddenly mattered for reproduction.

Of course, the concept of the healthy embryo came with a complexity of entangled issues that influenced the interpretation of this concept. For the Browns, it was Drs Steptoe and Edwards who defined what would count as healthy enough to be transferred. For women since then, many more decisions are involved. Parents can ask doctors to test embryos for structural health and to implant only the healthiest-looking embryos, defined in terms of most normal and most like those embryos that have developed normally before. (And fertility doctors claim a kind of quality control over which embryos are transferred, as part of the effort to boost IVF success rates.) Parents can also go further and ask for preimplantation genetic diagnosis (PGD) to test for a growing list of genetic 'diseases', selecting for implantation only those embryos that are free of the targeted genes. In some cases, parents can also ask for testing of sex and other non-disease features of an embryo. Considerable discussion has focused on embryo selection for therapeutic and enhancement purposes, and we need not repeat those debates here. But the Visible Human Embryo is a very different thing from the hidden embryo.

As mentioned before, IVF first succeeded in the context of recent innovations with recombinant DNA technologies. For some, this development raised the spectre of medical intervention in the 'normal' process of fertilization to produce genetically altered embryos. For others, the prospect for genetic selection against 'defects' was exciting and brought hope to families that felt burdened by hereditary 'diseases'. For still others, the issues are not so clear-cut: sometimes medical intervention would be appropriate for purposes of health, and other times it would be morally questionable; distinguishing these kinds of cases and the attendant reasoning has proven no easy task.

The technologies of the Visible Human Embryo have significantly influenced how we talk about human 'embryos'. Is an in vitro embryo an embryo in the same way as an in utero embryo is? Is it just a matter of geography, or does context matter constitutively? Are 'preimplantation embryos' biologically distinct from other embryos? Does a different moral status attach to such entities? What about 'spare embryos' (i.e. IVF embryos in excess of clinical need) that are potentially available for reproductive or research use by others? Are these biologically or socially different from embryos in utero? For many commentators, who would never dream of harming a human embryo once transferred to a woman, preimplantation embryos (spare or otherwise) are potentially fair game for interested parties.

IVF also brought new regulations and new interpretations of existing regulations. In the United Kingdom, the Warnock Commission produced a reflective report that has provided considerable guidance in a number of national and international policy documents starting

with the Human Fertilisation and Embryology Act 1990. This Act established the Human Fertilisation and Embryo Authority to licence fertility clinics and embryo research in the United Kingdom. In the United States, Congress has declined to pass legislation, which has led to considerable political manoeuvring, as different sides of different embryo-related issues have sought to get courts or commissions or presidents to rule or execute orders covering the use of human embryos (Green, 2001).

Another background factor in the United States was the Supreme Court ruling in *Roe v. Wade*. Though not explicitly about embryos and though the court declined to define when life begins or to define the embryo or fetus, the ruling clearly added to the climate in which other adjudications were made. The impression of *Roe* was that the embryo and fetus were protected while in the mother's body because they were ruled to be part of the mother and therefore under her control. Yet what of the embryo in the dish in the laboratory and in the clinic? Was this embryo also protected in some way? At first, it seemed that mothers held rights over these embryos as well, as their property, but with time that assumption was challenged in a diversity of ways. And in the absence of federal legislation, states have developed a patchwork of differing rulings that are inconsistent and confusing at best. Debates about the reach of laws to protect human subjects have dominated federal discussions related to embryo treatment; so too have concerns about commodifiable property, especially in 'custody' disputes about frozen embryos (e.g. Langley and Blackston, 2006).

The Visible Human Embryo has become a complex and highly contested object deeply embedded in its social context. The laboratory embryo is visible, sometimes viable, and no longer defined only as a primarily biological object but also as an object of reproduction – a dual identity that continues to this day in the context of human embryonic stem cell research. Concepts of the normal and the healthy embryo – for reproductive purposes – are new in the last few decades and are shaped largely by a combination of IVF and the public images of fetuses that people carry with them.

The Constructed Embryo

Finally, the cloning of Dolly and the initiation of human embryonic stem cell research have ushered in the period of the Constructed Embryo. Here we encounter questions not just about what is normal or healthy but also about what is 'natural'. The embryo is no longer a fixed natural object, but one in which scientists can rearrange or even replace cells, recombine genes, discover natural (and produce experimental) chimeras, remove, culture and experimentally differentiate cells and manipulate the internal and external environments to influence development. The embryo in this period is a highly malleable, literally and socially constructed and contested object.

The chant that 'life begins at conception' and the attempt to make the embryo a stable and comprehensible object is understandable in the face of all this change. Yet this approach is misguided. At least biologically, an embryo is still defined as the earliest stages of development. Yet it need not be the straightforward product of fertilization of a female egg cell by a male sperm cell. And it need not be genetically fixed but can be constructed, even out of cells taken from more than one embryo, as Beatrice Mintz showed very clearly in the 1960s, when she created mouse chimeras by combining blastomeres from different pigmented embryos; the resulting striped mice made the point very visibly (Mintz, 1967). Researchers can add genes to an embryo and can remove cells from a blastomere. Researchers can also remove the nucleus from an oocyte and fuse the oocyte with a somatic cell, catalysing early development either chemically or electrically; indeed, such somatic cell

nuclear transfer (SCNT, or cloning) experiments can be performed across species boundaries, as with rabbit oocytes and human skin cells, to produce entities that might yield human (or at least humanesque) pluripotent stem cells for research purposes (Robert, 2006; Minger, 2007). There are many different ways to construct embryos.

Constructed Embryos raise significant problems regarding nomenclature and regulation (see Baylis and Krahn, in press). What to call them, and how to regulate their creation – if at all – have vexed scientists and commentators alike (Robert, 2006; Newkirk, 2008). For example, is a 'part-human embryo' created via cross-species SCNT still a human embryo? What about an 'Altered Nuclear Transfer embryo' created by SCNT but with a twist – key genes required for successful implantation in a uterus are deactivated prior to SCNT, effectively eliminating the potential for development into a fetus or infant? Consider even an 'induced pluripotent stem cell' (iPS cell), created by genetic reprogramming of a somatic cell to exhibit the properties of pluripotency or perhaps even totipotency – is this resulting entity a new kind of embryo? (Kaebnick, 2008; cf. Cohen and Brandhorst, 2008). Those who propose creating such entities are banking on regulators to see a difference: if destroying embryos is wrong (or morally problematic or frowned upon), then perhaps these kinds of things, which perhaps are not embryos, can be destroyed with impunity. Whether such putative technical shortcuts around moral and regulatory problems actually work remains to be seen, but initial reactions have been equivocal at best (see, e.g., Melton, Daley and Jennings, 2004; see also Green, 2007).

Whether Constructed Embryos are embryos is one question worth asking. Whether and how they should be created are other questions demanding attention. And to what end embryos are constructed is yet another pressing concern. When IVF was first introduced, and throughout the heated debates thereafter about the naturalness of reproduction and the putative unnaturalness of IVF, one overriding concern seemed to take hold: that reproduction itself is so highly valued, and that childlessness is so morally and spiritually problematic (at least for some people), that the reproductive rationale trumps all. Indeed, this perspective is how scientists and doctors sold IVF: as a reproductive technology that could cure childlessness. IVF research, then, was sold as quality control and quality improvement: refinement of reproductive technology to cure childlessness more efficiently. Of course, not all embryos would be suitable for implantation and would have to be destroyed (or, once cryopreservation was introduced, frozen for later destruction in IVF research efforts). And of course, not all embryos would implant once transferred to a uterus. But these losses were seen as acceptable costs associated with a noble, trumping cause – reproduction.

Eventually, though, scientists wanted to create embryos not only for reproductive purposes but for research purposes, too. Although reproduction was a relatively easy sell, the same was not true of research. Creating IVF embryos for reproductive purposes was eventually taken in stride and has become a fully normal part of the twenty-first century. But with the identification of techniques for isolating human pluripotent stem cells from the inner cell mass of early embryos in 1998, came a new rationale for creating embryos: to facilitate research to harness the pluripotency of stem cells for therapeutic purposes (Thomson, Itskovitz-Eldor, Shapiro *et al.*, 1998). The isolation of the inner cell mass causes the death of the embryo; this type of pluripotent human stem cell research thus requires the destruction of human embryos. These embryos may be created by IVF or constructed by other techniques – whether specifically for research purposes, or (at least in the case of IVF) left over from reproductive efforts. At conferences, stem cell scientists mooted the benefits