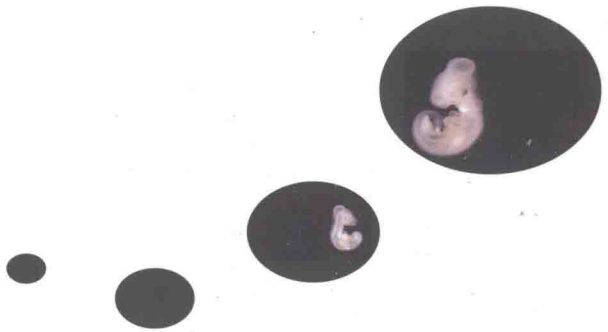
JANE MAIENSCHEIN

EMBRYOS UNDER THE MICROSCOPE

the diverging meanings of life



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THE DIVERGING MEANINGS OF LIFE

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Preface

When I have presented educational programs for federal judges under the auspices of the Federal Judicial Center or through the circuit courts, the judges have mostly started out without much science background—just as I started out without any significant political background. They mostly have not yet had to make court decisions themselves that have related to embryos, though a few have. But once they begin to hear about the issues that could arise and about the underlying biological facts, they become very interested and want to know more. They see that they are likely to have cases in the future for which understanding of what is at issue and what is at stake can help them judge wisely.

I also observed this eagerness for more information when serving as a senior congressional fellow, working in Congressman Matt Salmon's office during the United States 105th Congress in 1997 and 1998. Dolly, the cloned sheep, and then stem cell research both appeared during this time, and some of the initial responses were astonishing. One congressman wanted to outlaw cloning completely, but he had so little understanding of what is involved in the reproductive and developmental processes that his proposed bill would

have accidentally prohibited any mother from having natural identical twins. Others started with sensible ideas but then confronted constituents who argued with widely divergent but deeply held beliefs and little in the way of biological facts about stem cell research. I saw many people eager to learn and eager for reliable knowledge, yet they were caught in political and scientific confusion, sometimes caused or reinforced by the media.

Individuals who want to have a baby also need solid information. Those using fertility treatments have to make decisions about what embryos are, and they report often feeling that they do not have the right kind of information to make wise choices. This can lead them to rely on partial or simplistic ideas that are often just wrong biologically and may lead to unfortunate choices.

Members of the public are in a similar situation: inquiring minds do want to know, but it is not always obvious where to get reliable knowledge. Political discussions often serve as a sort of centrifuge, throwing the rhetoric away from the middle and toward the most extreme and farthest distant views, yet I optimistically feel that most of the time most people really like to be informed about science. We need interpreters to help us sort through the seemingly insurmountable piles of things to read, to present the story of science—and that is what this book will do.

This story is told historically, though not always strictly chronologically. Why do we study history? Because history can make science more reflective as well as make us better judges of scientific ideas and their implications. An old adage states that we study history to avoid repeating it. That makes sense in some cases: there are many unfortunate historical episodes we should try to avoid going through again. In other cases, if we understand the reasoning of the past, we may want to repeat those episodes, rather than avoid them.

History shows us that some scientists in the past addressed just the right questions, in just the right way, but they were hampered by limitations in technology, or choosing the wrong organism to

study, or insufficient finances, for example. In these cases, reflecting on why events took the turns they did can tell us a great deal. Scientists today may be able to go back with new tools and expanded knowledge in hand to productively pick up where those previous scientists had left off and perhaps make new progress.

Embryo research provides some especially compelling examples. By the 1950s, Robert Briggs and Thomas King had transplanted nuclei from one frog embryo into another and watched the resulting frog develop. John Gurdon then showed that in a smaller percentage of cases, he could transplant nuclei from adult frog cells into eggs and watch them develop into tadpoles. This work, the first cloning studies of animals, showed that researchers could reprogram cells through nuclear transplantation. Gurdon's results suggested that reprogramming was possible, and that adult differentiated cells (or at least their nuclei) could be changed into an undifferentiated state. But developmental biologists at the time relied on the major underlying assumption that cells develop in one direction only. They thought that once a cell is differentiated, it stays that way and cannot go backward. Gurdon's cloning example seemed like a special case, as textbooks of the time make clear that one-way differentiation was taken as given. This assumption turns out to have been wrong. It is worth revisiting this example and asking why researchers made the assumptions they did and what caused the field to change its collective mind.

In fact, those studying development had two deeply held assumptions before the late 1990s. First, they believed that differentiation works in one direction: once a cell becomes differentiated as a particular kind of cell, it will remain that kind. Second, they thought that the farther a developmental stage progresses, the more fixed and inflexible the developmental process becomes. These assumptions guided the thinking about embryos until 1997. Then we heard about the cloning of Dolly the sheep. The year after, we learned about the culture of human embryonic stem cells. These events provoked a

flood of research, which has changed both of the fundamental assumptions. In addition, parallel discoveries have challenged assumptions about the complex regulatory processing that guides gene expression. Furthermore, the changes in these underlying assumptions have raised the possibility of actually guiding the construction of embryos.

Historians and philosophers of science remind us of where we have been and help us to understand the underlying assumptions of scientific research at any given time, even when the researchers themselves have not articulated them. Historical and philosophical reflection can help illuminate why researchers made particular choices in the past, and that in turn can help us reflect on the choices being made today.[1]

Understanding the science alone, even in the context of historical perspective, will therefore not tell us what ethical considerations matter or what policy decisions to make. Yet knowledge about embryo research does provide a framework of reality that we are foolish to ignore. In his letter about the motion of the heavens to the Grand Duchess Christina, Galileo famously claimed that he intended his astronomical studies to tell us "not how to go to heaven, but how the heavens go." Historians will go on to point out that he did not really stop there—in fact, he made religious as well as scientific claims. Indeed, the two overlap at times in quite complex ways.

In this book, as in Galileo's case, understanding the biological facts about embryos tells us much about nature but not everything we need to know in order to think about social questions about nature and science. There is room for belief and values in making social decisions, and though the book's narrative tells the story of science, we return in the conclusion to reflections on larger implications.

Embryos under the Microscope

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Recurring Questions, Seeing and Believing

Looking at embryos without a microscope does not show much by itself. Human embryos are too tiny to see at all other than as teensy specks in a laboratory dish at a fertility clinic. Frog embryos are large enough to see, but not with much detail: a big egg cell divides into other cells and then gives rise to a tadpole, which swims around for a while then metamorphoses through a process of changing shape into a frog. Chick embryos are inside eggshells. Other species form in similar ways, and without a microscope to magnify the cells, we cannot see much of the intricate detail that is there in any of them.

In the past, the lack of empirical observed information required us to imagine what happens at the earliest stages of developing life. Some people (historically known as *preformationists*) believed that what exists from the beginning is a miniaturized version of the adult form. Others surmised that the form is not present initially, that instead something causes it to emerge over time, perhaps some special living or vital factor. The gradual changes seen in developing frogs would be evidence for such claims among those who thought about development in this second way (known as *epigenesists*), who imagined the form as emerging over time, one stage at a time. Alternatively, some in-between idea

might suggest that in the very beginning nothing is formed, yet that some predetermined information, or some special force, or even some kind of soul directs the material to take on just the right kind of form. Throughout history, philosophers advanced versions of all these different interpretations of how development occurs.

In all these cases, the embryo remained hypothetical. It was a metaphysically inspired entity, imagined based on underlying assumptions about what exists in the world and how it works. The data come from belief rather than empirically grounded knowledge. Thinkers would have little control over such a hypothetical entity because they would not understand the causes of its development. This hypothetical, metaphysical, imagined embryo has played a significant role in history, and this is the way that people thought about the animals they bred in agriculture and even about the early stages of their own gestating offspring.

Direct observation changed understanding of embryos. At first, led by Aristotle, a few philosophers inspected developing embryos without the aid of a microscope. By cutting a small hole in the shell of a chick's egg, Aristotle was able to watch form emerge from previously amorphous material. His observations emphasized an epigenetic rather than a performationist interpretation, but he could not see very much that way. Thus, the embryo still remained largely hypothetical until the introduction of the microscope in the late seventeenth century.

With the use of a microscope, better information about structure and changes in embryos came quickly. The period from the late seventeenth through the end of the nineteenth century brought accumulating knowledge and increased understanding of what embryos are and how they develop. With this information came new ideas about the meaning of life. By the end of the nineteenth century, researchers in the biological sciences had almost entirely rejected vitalist interpretations, had set aside nonscientific ideas of souls, and had come to emphasize the material basis of life.

By 1900, therefore, the embryo was a biological object for investigation. Yes, it is alive. Yes, it is the earliest stage of life. Yes, it is an individual, developing organism. But it is also a biological and material object to be studied, one that follows an internal logic and processes of its own and in response to its environment. This biological embryo became the focus of an experimental life of its own.

By 2000, it had become possible to analyze, deconstruct, reconstruct, and even construct almost from scratch the embryos of various species. Stem cell research, cloning, and synthetic biology are all methods for engineering embryos. The idea of engineering embryos had already appeared by 1900, but it took a century of research to gain the means for performing the work extensively. We are now in exciting times, with many prospects for using our knowledge of development to create new therapies and improve our quality of life.

The engineered or constructed embryo is very real—and it is also very frightening to some people. In some cases, confusion arises because so many people have never had the opportunity to examine embryos through a microscope. They have never seen the gradual emergence of new form, or the gradual appearance of the chick's beating heart. They have never seen the chromosomal actions of human cells dividing—perhaps even those of their own embryo in a fertility clinic's dish. Thus, many people cling to their metaphysically inspired, hypothetical imaginings about embryos because they simply do not know otherwise, although some do appear to find the hypothetical more comforting than the material reality.

Biological Basics

It is worth laying out some of the biological basics of what we now know about embryos before going any farther. Then the discussion will return to the scientific and public roles of embryos in historical and policy contexts. This book is about embryos generally and

how our knowledge of them has evolved over time, including the divergence of understandings and meanings imputed to embryos. The embryos of different types of organisms are not the same, sometimes differing entirely, other times only in detail. For our purposes, this book will look at research on different kinds of embryos for historical understanding and then for modern times focus on the human embryo. The historical discussion illuminates how we have arrived at our present understanding of the step-by-step process of embryonic change and the complexity of each embryo and its development. And first, let us look at the biological basics for human embryos as we have come to understand them.

In humans, the process of developing from a fertilized egg into an adult follows a typical sequence of steps (though there are many ways for the process to deviate as well). A woman develops egg cells, also called *oocytes,* in her ovaries; the majority of those oocytes will die over her lifetime. The best scientific estimates suggest that human female fetuses develop with millions of oocytes in their ovaries, and that they still have nearly 1 to 2 million at birth. By the time the woman reaches puberty, when she begins to ovulate and experience monthly menstrual cycles, she has an estimated 300,000 left. Each month brings the release of one egg (or occasionally more than one) such that throughout a typical woman's life she "uses" perhaps 300 to 400 of the oocytes she was born with. Recent evidence has suggested that women may produce more oocytes during life from special stem cells that persist into her later life, but we do not presently know how many or how this occurs in any detail. Again, the majority of oocytes just die.

Men produce millions of *sperm* as well, far more than the number of oocytes that women produce. In rare cases, one sperm will reach and fertilize one egg, typically after sexual intercourse or sometimes with technological assistance. Even here, only a few eggs become successfully fertilized, and each by only one sperm cell. Then even fewer begin to undergo cell division.

At each step, there is more loss and a low probability of continued development. What is amazing is that the process actually works as often as it does. When it does work, the one fertilized egg cell divides into two cells, those two divide into four, and those four into eight. (Figure 1.1). Then the cells start dividing at different rates, until they have multiplied into around 100 cells. At this point, the cluster of cells is called a *blastocyst*. The outside is a single sphere of cells that will become the placenta, and these surround an area that is partly hollow and partly filled with the *inner cell mass* composed of many cells. This is the point when the cells inside are first called embryonic *stem cells*.

In the earliest stages of cell division, all evidence suggests that cells are just dividing. In humans, the resulting embryo does not grow larger, and the cells do not yet undergo differentiation. That means that during these earliest stages, there is no evidence of significant expression of genes translating into characteristics in the developing organism. The cells merely mechanically divide and divide.

After this point in humans, the embryo has to become implanted in a uterus to be able to continue developing. At this point also, significant gene expression begins. The model from what many consider as the golden era of genetics in the 1950s laid out what was called the central dogma, according to which the DNA (deoxyribonucleic acid) molecules in the chromosomes make smaller molecules called RNA (ribonucleic acid), which can move out and cause the production of proteins: DNA to RNA to protein. This is simple and straightforward, and although not complex enough to describe the developmental processes fully or accurately, it provides a good start for understanding the processes involved.

Gradually, developmental biologists uncovered the complexity of the processes by which genes get expressed. A great deal of regulation of the process occurs through a mix of inherited, internal, and environmental conditions that we are only just beginning to understand fully. Researchers have also added to our understanding of the