

September 28, 1999

In the Ethics Storm on Human Embryo Research

By NICHOLAS WADE

NASHVILLE -- On the white paper tablecloth, Brigid Hogan is sketching a diagram with the children's Crayolas the restaurant has thoughtfully provided. The daughter of two artists, she draws rapidly and precisely. The structure of an embryonic lung billows across the table. Words like "sprouty," "breathless," "branchless," playful names for the genes that control the process, appear alongside arrows and curlicues. Watching this gentle English biologist reach for another Crayola, it is hard to believe she could ever occasion a threat, let alone one Congress has deemed so severe that it has thrice passed a law to thwart it.

A leading expert on the embryology of the mouse, Dr. Hogan was the scientific co-chairwoman and principal author of a National Institutes of Health report on human embryo research.

The report, published in 1994, presciently described the benefits to be expected from the study of embryonic stem cells, the primordial human cells that were first isolated last November, and it said biologists should be allowed to derive the cells from the surplus embryos created in fertility clinics. Some biologists hope the cells will provide a universal repair kit for human tissues.

The idea of destroying human embryos, even surplus ones, was daring enough, but the report went on to recommend letting embryos be created by mixing eggs and sperm in a dish, a procedure that could help treat infertility.

President Clinton swiftly repudiated the notion of creating human embryos for research purposes. And Congress was so perturbed by the report that for the last three years it has specifically forbidden the National Institutes of Health to pay for any research in which a human embryo is destroyed.

The agency now believes it can legally finance researchers to use the cells, though not to derive them, under rules recommended by a group of experts, including Dr. Hogan. The guidelines are expected to be issued imminently but abortion opponents hope to have Congress override them.

A clash of competing values was perhaps inevitable as biologists started to part the veils around the mystery of life's earliest moments. The report by Dr. Hogan and her colleagues, who included ethicists as well as biologists, precipitated the maelstrom because it was a ringing scientists' manifesto, a public declaration of the various types of human embryo research that were about to become technically feasible and the medical benefits to be expected from each.

Dr. Hogan works at Vanderbilt University Medical Center in Nashville and holds a coveted fellowship from the Howard Hughes Medical Institute, a munificent patron of biomedical researchers.

In her office overlooking a graceful courtyard on the Vanderbilt campus, she seems far removed from the political fray set off by her panel's report.

"I think it is a tremendous shame that people funded by the National Institutes of Health cannot work on embryonic stem cells," she said. But she has no present plans to do so herself. Apart from one foray into human embryology, an attempt to derive stem cells from fetuses, her chief interest has always lain with the mouse.

As a scientist, her purpose is to understand how embryos develop. For the most part, that requires genetic manipulations that would be unacceptable with human embryos. But because people seem to be constructed with a very similar set of genes, research by mouse embryologists like Dr. Hogan is laying the groundwork for understanding and repairing the many human imperfections caused by defects in the embryo-shaping genes.

Dr. Hogan's interests in embryos are esthetic as well as practical. Ever since she was a girl growing up near High Wycombe, a town 28 miles northwest of London, she has viewed embryos as things of particular beauty. "I carry a

picture of a mouse embryo in my wallet to look at if I'm feeling low, like people carry pictures of their family," she said.

She studied biochemistry at Cambridge University and did postdoctoral work at Massachusetts Institute of Technology on sea urchins. But the genetics of sea urchins are not well understood, and besides, she said, "You don't feel that warmly about the sea urchin embryo." On returning to England, Dr. Hogan switched to the mouse, which was then becoming easier to study because of new advances.

Although scientists are supposed to be able to reproduce another's work by following the recipes given in published articles, there are often details of technique that never get written down. Dr. Hogan soon realized that there was a whole body of arcane lore, known only to specialists, about how to mate mice and manipulate their embryos. During a meeting at the Cold Spring Harbor Laboratory on Long Island, a leading teaching center for biologists, she mentioned to its director at the time, James Watson, the idea of holding a course there to teach researchers how to do mouse embryology.

Dr. Watson abruptly left the table where they had been talking, leaving her to wonder what she could have said to offend him. But a few minutes later, the time necessary to visit his business office, Dr. Watson returned, saying, "It's all organized." Dr. Hogan began teaching a summer course, now in its 16th year.

Dr. Watson's enthusiasm was not mirrored at the National Institute of Medical Research in London, where she then worked.

"At Cold Spring Harbor, everything is organized to get things done," she said. "In the N.I.M.R., people thought you were a nuisance if you asked for anything."

During Christmas vacations, the institute's building was closed for two weeks, and those who wanted to work had to bring in their own heaters. Dr. Hogan recalled how her ankles would burn while the rest of her shivered. She decided one Christmas Eve that she could not be competitive in such circumstances. Writing round to friends, she heard of a job at Vanderbilt, where she moved in 1988.

With a group of 11 people, including graduate and postdoctoral students, she is trying to reverse-engineer the mouse by analyzing the genetic program that guides its development from an egg. Mouse researchers now have many powerful techniques at their disposal. They can remove a gene, creating a strain of "knock-out" mice that by their physiological defects may reveal what the gene is meant to do. Or they can replace a gene with one that makes a blue stain that shows when and in which tissues the gene is active.

With colleagues at Vanderbilt and elsewhere, Dr. Hogan has found that a particular gene, known as BMP-4, must be switched on if the embryo is to set aside germ cells for the next generation of mice.

She is also studying the development of organs like the lung and the lens of the eye.

Both require interactions between cells belonging to two of the three sheets of tissue of which the early embryo is formed.

These interactions are governed by specific genes, whose roles she is trying to define.

Though she focuses on the mouse, Dr. Hogan is keenly interested in how the techniques she and colleagues have developed may be applied in medicine.

Now that human embryonic stem cells have been isolated, they allow human embryos to be manipulated with the same mastery as mouse embryos, although of course most of the changes made to mouse embryos would be ethically unacceptable in humans.

Dr. Hogan agrees with researchers who believe that human embryonic stem cells are likely to be useful in repairing ordinary tissues in adults or in a fetus. But she opposes the use of altered embryonic stem cells to make changes to an individual's germ line, as is done routinely in making knock-out mice.

"I think the technique is far too risky and is unlikely to ever be perfected to the stage when it is absolutely 100 percent reliable, which is what one would have to insist on," she said.

Sitting at a dual-eyepiece microscope, Ray Dunn, one of Dr. Hogan's graduate students, shows a visitor the magical moment when the mouse embryo changes from a blob to a being. Up to six days after fertilization, the embryo is a tiny white opalescent cylinder, still far more like an egg than an animal. But by the eighth day it has billowed out into a tier of buds and whorls, visibly destined to form head, heart, limbs and tail. Human embryos look much the same, though they have a more flattened-out appearance.

Though embryologists are far from being able to understand how a mouse or human is put together, the problem does not seem insoluble. Five families of signaling genes, many used over and over again at different stages of development, seem to control a major part of the mouse embryo's development.

When all the developmental genes and their functions are known and entered in the databases, won't the mystery of life be dispelled and its awe destroyed? Dr. Hogan doesn't think so. The embryo, she said, "is to me the most beautiful thing in the world, quite exquisitely beautiful, and the idea that one could eventually describe how it is formed and grows just in terms of molecules and genes and pathways doesn't detract from the beauty at all, makes it more awesome, in fact."

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