Rules on Embryo Research Due Out

Controversy is sure to follow as an NIH panel gets set to recommend to Harold Varmus the first guidelines for funding research involving human embryos.

The muggy summer of 1994 is cooling off in much of the country, but the National Institutes of Health (NIH) may not be in for much relief from the heat. Director Harold Varmus is about to go public with the first proposed rules governing the use of human embryos in research. Based on interviews with members of a panel advising Varmus on embryo research as well as a reading of the panel's proceedings, *Science* would predict that broaching this most explosive of issues will guarantee NIH a sizzling autumn.

Publicly funded research on human embryos in the United States has been on hold for more than a decade, largely because the politics of the abortion debate led previous administrations to ban such research at NIH. But in the last year both President Clinton and Congress have signaled that the moratorium should end, and on 27 September Varmus plans to make public guidelines recommending which embryo studies NIH should fund and which it should shun.

The final rules to be adopted by NIH will be based on, though not necessarily ratify, these recommendations, which were drafted by an advisory panel led by Steven Muller, president emeritus of Johns Hopkins University, policy chair Patricia King of the Georgetown University Law Center, and science chair Brigid Hogan, a biologist at Vanderbilt University.

The panel and its chairs have been sensitive to the concerns of both advocates and opponents of this kind of research. According to committee member Mark Hughes, a leader in genetic embryo testing who this month moves from Baylor University to NIH and Georgetown University, "the panel is trying to be open to the concerns of a large segment of the population," which feels science may be moving too rapidly into once-forbidden territory. He added: "We're saying basically there's so much that we don't know—let's just start slowly."

But even as some experimenters chafe under this go-slow approach, it won't inoculate the panel against attacks from the right-to-life movement. Those attacks may well focus on what is likely the most controversial element in the panel's report. Although the 19-member panel is still at work, *Science*'s interviews of key panel members reveal that the panel's version of the guidelines permit creation of a limited number of human embryos for research purposes.

Richard Doerflinger, associate director of the National Conference of Catholic Bishops Secretariat for Pro-Life Activities in Washington, D.C., seized on this issue to denounce the entire NIH rule writing effort. Speaking at the final open session of the panel on 21 June, Doerflinger said that there can be no "legitimacy of nontherapeutic experimentation on live embryos." There is "nothing in existing law or legal precedent," he continued, "that says the embryo outside the womb deserves less protection" than the unborn fetus.

NIH is trapped between long-frustrated researchers who are counting on getting a green light and conservatives like Doerflinger and Representative Robert Dornan (R) of California, who wrote a sharp letter to Varmus demanding to know on what authority Varmus was revising the embryo research guidelines. And NIH could be in for a grueling fall. Even before the Muller panel presents its conclusions, a lawsuit has been filed by a group opposed to genetic screening of embryos citing what they see as "conflicts of interest" on the part of panel members likely to be funded by NIH in this field.

The panel is born

Varmus assembled the Human Embryo Research Panel last January. The main reason for creating it, Varmus said at the time, was to help him decide what to do with "several applications for support" from researchers who wanted to begin embryo research in the more tolerant atmosphere of the Clinton Administration. Varmus cited a clause in the 1993 NIH reauthorization bill, lifting a decade-old embargo on human in vitro fertilization (IVF) experiments, as authority for moving forward. But, as he later wrote in response to Dornan's letter, "we did not want to proceed without broadly considering the moral and ethical questions."

The Muller panel met for the first time on 2 February and has been deliberating ever since. By the end of last week, according to panel members who spoke with *Science*, the group had laid down a general framework and chosen most of the rules it intends to adopt (see box). Because the panel was divided on some issues, a few topics were being voted on as *Science* went to press. In spite of these

MULLER PANEL'S GUIDELINES—IN GESTATION

FUND NOW, WITH NIH CASE-BY-CASE APPROVAL

- Research on existing, unused in vitro embryos, up to 14th day
- Limited creation of in vitro embryos for baseline data, but only for "compelling" research
- Cell extraction (blastomere biopsy) from embryos before implantation
- Derivation of cell lines from existing unused embryos
- Maturing unfertilized eggs (parthenotes) for research

NEEDING FURTHER CONSIDERATION

- Use of fetal oocytes to create embryos for research only
- Research on existing embryos beyond 14th day to neural tube closure
- Cloning by blastomere or blastocyst separation, research only
- Use of existing embryos for research when one progenitor was an anonymous gamete donor who received monetary compensation, or cannot be located to give explicit consent

NOT ACCEPTABLE

- Transfer of human embryos to animals for gestation
- Transfer of research embryos or parthenotes to humans
- Research on embryos beyond neural tube closure (18th day)
- Twinning (separation of blastomeres) for gestation
- Cloning of embryos by nuclear transplantation
- Creation of human-human or human-animal chimeras
- Creation of embryos strictly for research material, e.g., stem cells
- Cross species fertilization with human gametes, except clinical testing of sperm penetration (with hamster eggs)
- Transfer of embryos to cavity other than uterus
- Sex selection of embryos, except to prevent x-linked diseases
- Use of sperm, eggs, or embryos from donors who did not give explicit consent to research
- Use of sperm, eggs, or embryos for which donors received more than reasonable compensation

undecided areas, by mid-August the panel had settled on its main guidelines.

The panel plans to recommend that research be permitted on "spare" embryos collected at fertility clinics. These spares would otherwise be discarded. They accumulate because IVF clinics produce excess embryos to minimize the number of treatment cycles a woman must go through in therapy. The panel calls for creating a standing advisory board reporting to the NIH director to decide who should have access to the "spare" embryos. The new board's task would be to review every research protocol, checking scientific quality and ethical suitability. The Muller panel has decided, for example, that no embryos may be used if the donors of sperm or eggs did not give explicit consent for the use of their embryos in research.

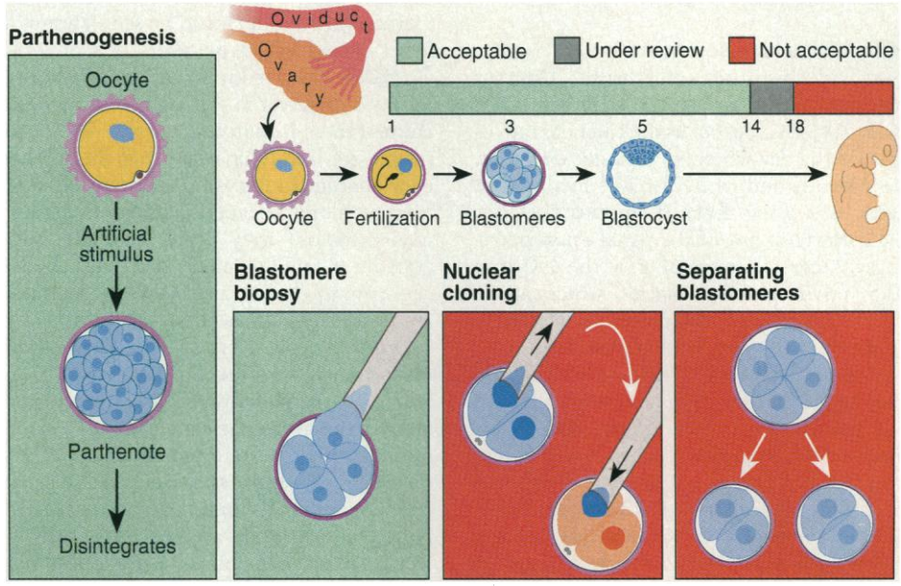
As a general rule, the panel is planning to say that all research will have to be conducted by a "qualified" scientist in an "appropriate" research setting. Each experiment will have to be well designed; it will have to be supported by prior animal studies and research on human gametes; and it will have to demonstrate some clinical benefit. One overriding goal is to keep the number of embryos used as low as possible.

Embryonic controversy

The Muller panel is also poised to approve the concept of creating a limited number of new embryos from donated eggs and sperm expressly for research. None of the embryos would live long, since the panel adopted as a provisional standard the widely used international rule that research must stop at the 14th day after fertilization. Panel members added a refinement, however: research may continue until appearance of the "primitive streak," the first indication of a nervous system. That appears to occur after the 14th day, but only by experimenting will researchers learn just how long after the 14th day it does actually occur. After further review, the panel says, NIH may want to permit research up to the point of neural tube closure, which could come at the 18th day or later. But in no case should research go beyond neural tube closure, the panel has concluded, and none of the research embryos should be transferred to humans for gestation.

Why is the panel willing to propose something guaranteed to ignite a firestorm? One goal is to permit detailed analysis of oocyte maturation and fertilization, which results in a live embryo. Yet another reason for creating new embryos in the lab rather than relying solely on the IVF "spares," as panel member Hogan explained during an open session on 22 June, is that most of those stored in IVF centers may be abnormal, since they came from people with problems in conceiving.

The panel also overwhelmingly approved the use in research of "parthenotes": human eggs that have been made to grow without fertilization. In the absence of "genetic imprinting" by sperm—which subtly alters the embryo's DNA—the parthenote dies. Even in their short lives, however, parthenotes could yield valuable information on cell division and imprinting, according to Jonathan van Blerkom, a molecular biologist and IVF clinician from the University of Colorado, Boulder, who was commissioned by NIH to review the relevant science for the Muller panel.



Fertile grounds for debate. The NIH panel's decisions were based on timing with respect to fertilization *(above)* as well as on general ethical considerations *(below)*; as a result of the latter, "twinning" by separating blastomeres was ruled out along with some other procedures.

Kenneth Ryan, former obstetrics and gynecology chief at Harvard's Brigham and Womens' Hospital, warned the panel that some people will regard the making of parthenotes as "ghoulish." Indeed, witnesses at the panel's open sessions and letter writers objected to it strongly. Nevertheless, many panel members, including chairman Muller, viewed the use of the unfertilized parthenotes as a good way of limiting reliance on embryos. Reacting to hostile comment, NIH director Varmus has written to Dornan that NIH hopes to "clear up" the "confusion and misunderstanding" about parthenotes by educating the public.

Divisions on the panel

Not every innovative research path received blanket endorsement. One that did not involves taking cells from embryos to create permanent cell lines. Hogan strongly advocated moving forward with this research; van Blerkom also saw it as promising, explaining that embryonic stem cells are the subject of intense study because of their unique properties. These cells seem to be ignored by the immune system and thus are not rejected by the host as alien. They can proliferate rapidly, and have the potential to develop into essentially any form of tissue, bone or cell. Many researchers think they could one day be used, as van Blerkom wrote, to treat "a wide range of important human diseases," including loss of bone marrow, dysfunctional liver, and loss of neural function in the brain and spinal cord.

On the other hand, as Georgetown attorney Patricia King, the panel's policy chief, observed, there was "substantial opposition" to developing these permanent cells lines among panelists on ethical grounds. As *Science* went to press, the panel had voted to allow derivation of stem cells from existing embryos, but debate was continuing.

In other areas, the panel gave approval—but only with reservations. One area was blastomere biopsy, which involves removing a cell or two from an early-stage embryo and using tests to examine DNA in the cell for defects. A sign of the growing prominence of this method is that Hughes, a leading practitioner, has been recruited to the National Center for Human Genome Research at NIH to head a new branch of reproductive genetics. He will also have a clinic at Georgetown University. Hughes and colleagues in England used it to help a couple with an inherited risk of cystic fibrosis screen out an embryo that carried two copies of the gene for the disease and select an unaffected embryo, which was implanted, leading to the birth of a healthy girl. Hughes and others hope to use the method to test for Duchenne's muscular dystrophy, Tay-Sach's disease, Lesch-Nyhan syndrome, and other diseases.

Under rules adopted by the Muller panel, blastomere separation for biopsy would be

permitted. (However, separating cells to duplicate an embryo for implantation would be forbidden; the panel considered it morally unacceptable.) Hughes is pleased his work has been approved. But he notes an irony: If the guidelines had been written before the procedure was tested, "they wouldn't have allowed it, because you wouldn't know if taking a blastomere from an embryo was going to create a birth defect." He concedes the new rules may be arbitrary in favoring some areas of research while discouraging others, like a "two-edged sword."

Will politics take command?

National Institutes of Health Director Varmus need not accept these recommendations at face value, but as the calendar moves toward the day when he must decide which he supports and which he will modify, the tension is rising. Even if Varmus does not back down on any of the panel's new openings for research, researchers at the 250 or so U.S. private fertility clinics, which aren't controlled by federal regulations, are likely to see the new rules as too restrictive.

David Adamson, a leading fertility researcher in Palo Alto, California and chair of the research committee of the Society for Assisted Reproduction Technology, says he's concerned that "we not develop a national policy that is more politically oriented than scientifically justified." Adamson argues that "we are really just scratching the surface" of new methods for helping infertile couples; it could be a mistake and an unfair burden, he thinks, to saddle the field prematurely with a lot of detailed restrictions.

From the conservative side, meanwhile, comes the International Foundation for Genetic Research, which despite its name seems eager to discourage some types of genetic research. Located in Pittsburgh, this group, which claims to represent parents of children with birth defects, filed a federal suit in June against Varmus, Health and Human Services Secretary Donna Shalala, and members of the Muller panel, charging that panel members have conflicts of interest and should be prevented from giving NIH any advice.

Specifically, the suit argues that panel members like Hughes, who is developing genetic screening methods for IVF clinical use, and Hogan, who has a stake in a company that hopes to produce cell lines from aborted fetal (not embryonic) tissue, should not be shaping federal policy. Hughes responds that it is hard to imagine how NIH could develop policy without help from researchers who know the most about the subject—and they are just the ones who are likely to be funded by NIH and have investments in biotech. Hogan argues that her patent for stem cell production has no application in embryo research and presents no conflict.

Academic scientists find themselves caught in the middle, taking a moderate and pragmatic point of view. Many feel, as Hughes says, that by laying out specific guidelines, the NIH panel "legitimizes the science in a way that hasn't been done before." These researchers hope that the public, seeing that scientists have adopted a measure of self-restraint, will be ready to offer funds after a long dearth.

In the end, though, the limits on embryo research may be set by Congress, not NIH. A warning shot was fired by California's Dornan on 16 June, when he sent Varmus a letter signed by 35 members of Congress. They demanded to know Varmus's authority for revising research. "Congress has not examined these initiatives, and the American people are largely unaware that the NIH is even contemplating using their tax dollars to fund such bizarre experiments on living human embryos," they wrote. And they suggested the panel members had conflicts because many "seem interested in potential grants for these kinds of experiments."

Varmus replied on 21 June that NIH's mission includes attacking "infertility, pregnancy loss, genetic disease, and cancer" and all these areas "might benefit from research involving the ex utero human embryo." As for conflicts of interest, Varmus replied that "no individual was found to have a disqualifying conflict...that would significantly affect, or, in our judgment, give the appearance of affecting the member's duty to participate impartially" in weighing ethical issues.

An aide to Dornan says the congressman was not satisfied with this response; Varmus, he says, will soon get another letter. For its part, NIH appears to feel the best hope of winning broad support lies in informing the public about the potential health benefits of embryo research. As Varmus wrote Dornan, NIH thinks a great "misunderstanding" may have fomented opposition to certain research tools, such as the use of parthenotes. To help educate the public about the subtleties of embryo research, NIH is planning a special media briefing a week before the release of a draft report on 20 September.

By then, the air inside Washington's Beltway may be cooler. But it remains to be seen what the climate will be like in the halls of power. Biologist Van Blerkom recalls that when he made his presentation to the Muller panel, there were "three very big guys wearing big crosses" sitting in the back row. They reminded him, he says, that there are dimensions to the embryo research controversy that have not fully surfaced yet. Is the research community, he wonders, truly prepared for the "enormous debate" that may erupt when new guidelines for embryo research are issued? We will find out soon enough.

–Eliot Marshall

ASTRONOMY

Europeans Push Ahead With Disputed Observatory

The eight-nation European Southern Observatory (ESO) decided last week to press ahead with its Very Large Telescope (VLT) project in spite of a gathering storm in Chile, where the instrument is scheduled to be built. The VLT, a set of four 8-meter telescopes to be used as a single instrument, will be the world's largest telescope when it becomes operational, which ESO hopes will be soon after 2000. Those hopes could be dashed, however, by a dispute over ownership of the site atop Cerro Paranal in northern Chile and by a history of poor relations between ESO and Chilean astronomers and workers.

But ESO's governing council signaled its determination to stick to the original schedule by giving the go-ahead to ship parts of the first rotating dome in September or October. "We're showing our good faith by putting 500 tons of steel on a ship to Chile," says ESO director general Riccardo Giacconi. "It's risky, but then there is a risk that timidity would damage the project." The council is hedging its bets, however: It also asked the organization to continue looking for alternative sites for the VLT. "If a catastrophic development occurs, we can always remove the equipment [from Chile]," says the council president, Peter Creola of Switzerland's Federal Department of Foreign Affairs.

The clear, dry air above the Atacama desert in northern Chile makes it one of the best sites in the world for ground-based optical astronomy. In the 1960s, three foreign-administered observatories were set up to take advantage of these conditions: the Cerro Tololo Inter-American Observatory (CTIO), one of the United States' National Optical Astronomy Observatories; ESO's La Silla observatory, which now has 14 telescopes; and Cerro Las Campanas, set up by the Carnegie Institution. Claudio Anguita, former director of the University of Chile's department of astronomy, says that Chilean astronomers have had happier dealings with the U.S. observatories than with the European one.

The CTIO, Anguita says, signed an agreement with the University of Chile guaranteeing its astronomers 10% of the observatory's viewing time. And Chile has now become a partner in the Gemini project, which will link twin 8-meter telescopes, one at Mauna Kea, Hawaii, and one at CTIO. "We feel at home [with CTIO]"