Gene Mutation Link With HIV Resistance

Joan Stephenson


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At the Cloning Circus Sideshow Abounds, While Scientists Seek a Wider Audience

Brian Vastag

WASHINGTON—The scene inside the National Academy of Sciences auditorium on August 7 resembled a daytime talk show. Banks of television klieg lights baked the stage, where astonishing revelations and wild gesticulations garnered hoots and jeers from the audience.

Early in the day-long event, one of three would-be human cloners broke off an argument and exclaimed, “People think we are mad scientists. We are not!” Some of the two dozen recognized experts in reproduction, genetics, and ethics sharing the stage sighed at the antics of Panay Zavos, PhD, director of the little-known Andrology Institute, a commercial research facility in Kentucky. His sparring partner, from the well-known Whitehead Institute at the Massachusetts Institute of Technology, Rudolf Jaenisch, PhD, remained calm and posed the first of the day’s many rhetorical questions. “Is a cloned animal that looks normal really normal? Animal embryonic development can continue despite genetics problems which may appear later.”

Zavos, who had been trying to interrupt Jaenisch, leapt from his chair. “We came here for discussion and I think we deserve an opportunity . . . ” he began.

“You’ll have an opportunity!” roared moderator and agitated peacekeeper Irving Weissman, MD, a cellular biologist from Stanford University School of Medicine.

Indeed, Zavos and his partner, Severino Antinori, MD, got many opportunities. Hordes of TV crews, correspondents, and photographers descended on them during breaks. Reporters milled about the stage, attempting to identify the various combatants.

By the next morning, the announcement by Zavos and Antinori that they would clone a person before the end of the year had traveled around the world and back, diverting attention from what was meant to be a serious scientific workshop, and eclipsing the message delivered by the mainstream scientists. For most of the day, the world’s foremost animal cloners had presented reams of data supporting their case that high rates of late-term miscarriages, early deaths, and severe deformities led to the obvious conclusion that attempts to bring a cloned human embryo to term should be punished as criminal. They promised to issue a report by the end of this month.

CONVINCING EVIDENCE

Their evidence was convincing. To date, hundreds of apparently normal sheep, mouse, pig, goat, and cow clones have been born, while efforts to clone rabbits, rats, cats, dogs, horses, and monkeys have failed. No one knows why. Last year an Asian gaur, an endangered ox, was cloned and carried to term by a cow in South Dakota. The calf died within 48 hours after delivery, but researchers at Advanced Cell Technology in Worcester, Mass, said dysentery caused the death, not complications related to cloning.

But the success rate for the standard technique, in which the nucleus of an egg is replaced with one from a donor cell, is dismal: typically, 1% to 3% of nuclear transfer oocytes survive uterine implantation, gestation, birth, and early life. The success rate for the first cloned mammal was just 0.4%. At the Roslin Institute in Scotland, 277 sheep eggs were cloned and 29 developed into viable embryos; these were implanted into 13 ewes. Only Dolly came to term. Complete information is accessible at http://www.roslin.ac.uk.

Most recently, a modified technique called recloning—transplanting the
nucleus of an adult cell into one egg and then to another—has pushed the success rate to 5%, although the reason is unknown.

“The losses at each step are extraordinarily large,” said Alan Colman, PhD, research director at PPL Therapeutics Inc, Blackburg, Va, the firm that funded the cloning of Dolly the sheep. In contrast, about 25% of naturally fertilized human eggs produce a live birth. Most of the rest do not reach the sixth week of pregnancy. But with experimental animal clones, many more spontaneous abortions occur during the third trimester. “Who wants to see human fetuses aborted very late in gestation, and abnormal as well?” Colman asked.

**PLACENTAL PROBLEMS**

Malformed placetas account for many of the cloning miscarriages, said Jonathan Hill, PhD, assistant professor of theriogenology (a newly coined term meaning the study of animal reproduction) at Cornell University College of Veterinary Medicine. In cows, a normal placenta sprouts 100 or so placental membranes (knobs of tissue connecting the placenta and uterus) that exchange nutrients and wastes. Placentas of cloned fetuses tend to have many fewer, leading to diminished oxygen and nutrient flow. One cloned calf Hill examined was born with a placenta that had just 14 attachments.

Hill said that about one third of the successfully implanted cloned embryos in a study involving cows survived to gestation day 30—a rate similar to that seen in natural reproduction. But half of those early survivors did not reach day 90, a much higher rate than would be seen in natural reproduction. (Cows gestate for about 9 months.) Many of these fetuses were scrawny—half as large as normal. “They just fade away. We watched it on ultrasound,” said Hill.

Paradoxically, of the cloned fetuses that made it into the third trimester, most were larger than average size, often from edema, which further reduced placental nutrient exchange. “The animals kind of outgrew their placenta,” said Hill.

That finding jibes with the most consistent abnormality reported: Clones that survive birth tend to be larger than normal (see accompanying story). It happens so frequently that in the 4 years since Dolly was introduced to the world, scientists have coined the term large offspring syndrome (LOS). Lung, heart, and liver defects often accompany LOS; sometimes they appear in normal-sized clones. Brain, tongue, and other deformities have also been reported.

Lung problems are disturbingly common. One fourth to one half of all newborn clones succumb to pulmonary distress, said Ryuzo Yanagimachi, PhD, the world’s leading mouse cloner and a professor of reproductive biology at the University of Hawaii School of Medicine. “They're basically hypoxic at birth,” he said. Mice surviving to adulthood appear normal, he added, and some have lived to the ripe old murine equivalent of age 95 years.

One lamb cloned recently at the Roslin Institute, Scotland, “looked fine, ate, and moved around okay, but it hyperventilated and panted a lot,” said Ian Wilmut, PhD, Dolly’s cloner. The Roslin staff euthanized the lamb after 12 days out of compassion. An autopsy revealed thick, tough muscle constricting blood vessels in the lungs, cutting oxygen flow. “But what if it’s a baby?” Wilmut asked. “How would it be treated?”

With that question left hanging, Wilmut emphasized that he and most, if not all, of his colleagues expect similarly poor results in people. For human cloning to succeed, he concluded, “we need a step as big as the one that produced Dolly.” Meanwhile, Wilmut and colleagues agree that current problems make the thought of cloning humans repugnant.

### Epigenetics Is Seen as Possible Key to Cloning

**Brian Vastag**

WASHINGTON—Sheep cloner Ian Wilmut, PhD, of the Roslin Institute in Scotland, recently said that for human cloning to succeed, “we need a step as big as the one that produced Dolly” (see accompanying story).

If that step ever comes, it will likely involve the nascent field of epigenetics, literally, “after genetics.” With the Human Genome Project nearing completion, scientists at the edge of biology are surveying enigmatic cellular processes that are perhaps as fundamental to life as DNA itself.

Although many of the estimated 40,000 genes have been spelled out to the last A, C, T, or G, researchers have only a shaky understanding of how and why they switch on and off. Thanks to microarray analysis, they know that patterns of gene expression shift like the colors of a kaleidoscope. The spiraling hues depend on where the cell lies in time—developmentally or per the cell cycle, and space—whether in the heart or the brain.

Strides made in the past few years point to proteins that bind and wrap DNA into chromatin, the scrunched-up threads located in cell nuclei. Enzymes and even RNA regularly interact with
this complex. These chaperone molecules can tag genes needed by the cell, pry open the appropriate stretch of chromatin, and initiate protein production. They can stitch chromatin shut to silence a gene.

New research suggests that variations in this epigenetic machinery can be inherited, but not via DNA. No one knows how, but in a turn that would drive Mendel out of the pea patch, it seems that another means of inheritance exists. In a recent review, experts propose a system called the “histone code”—histones being proteins involved in forming chromatin. According to the authors, this code “represents a fundamental regulatory mechanism that has . . . far reaching consequences for . . . both normal and pathological development” (Science. 2001;293:1074-1080). In other words, it may be just as important as DNA.

**A BLACK BOX**

Epigenetics and cloning meet in a newly cloned zygote. There, the transferred nucleus of an adult cell undergoes a remarkable reprogramming. The black box of cloning, this cellular prestidigitation transmutes, say, an ordinary skin cell, like the millions that are shed every day, into a potential life.

Through an epigenetic process not yet understood, the egg resets genetic switches inside the donor nucleus, directing its 6 ft of coiled DNA to stop acting like that of a skin cell and start acting like that of an embryo. It’s like rolling back the odometer of a used car to zero—and actually getting a new car.

With natural reproduction, this reprogramming transpires over months and years as sperm and egg, respectively, mature. After a sperm wriggles through the zona pellucida, some mysterious apparatus in the egg’s cytoplasm completes the reprogramming. The job is crucial. Each stage of fetal development triggers a unique cascade of genes, switching on and off in precise choreography. If the reprogramming goes well, the zygote gracefully grows into an embryo, a fetus, a person.

In nuclear transfer cloning, reprogramming is allotted precious little time—minutes to hours. When a micropipette injects a donor nucleus into a waiting egg, the donor’s genome retains its old, worn configuration. It knows only how to make other cells of its kind, whether skin, muscle, or something else. Asking the nuclear material to engender an embryo is akin to telling a grandfather to repeat puberty. Unless reprogramming quickly succeeds, the opportunity for disaster is huge (see accompanying story).

Led by Wilmut and a handful of others, cloners are beginning to understand what goes awry in clonal embryonic wrecks. In particular, they’re finding problems with so-called imprinted genes, which are exquisitely sensitive to epigenetic reprogramming errors.

These renegades defy biological convention. Their discovery nearly two decades ago shocked biologists. While the vast majority of genes operate with two alleles, one from each parent, imprinted genes function with just one allele. The other is silenced by epigenetic machinery, most likely during early embryo development. To date, some 50 imprinted genes have been found in mice and humans.

With just one working allele, a single mutation can trigger serious problems, as can errors in imprinting itself. Already researchers report strong links to severe congenital diseases such as Prader-Willi, Angelman, and Beckwith-Wiedemann syndromes. The latter is characterized by increased risk for rare cancers (in particular Wilms’ tumor), fetal overgrowth, and enlarged tongues and organs.

Those problems sound familiar to animal cloners. Large offspring syndrome (LOS) appears in perhaps 30% to 40% of cloned animals, who manifest overgrowth traits similar to those seen in children with Beckwith-Wiedemann syndrome (Rev Reprod. 1998;3:155-163).

**A SINGULAR PATH**

Work on this imprinting link has taken Duke University Medical Center’s Randy Jirtle, PhD, down a path that has resulted in his angering some prominent cloning experts. In August, Jirtle published an article in which he concluded that cloned humans would be unlikely to experience LOS. An accompanying press release claimed that people might be easier to clone than animals. The story attracted widespread media attention, leading to characterizations of Jirtle as pro-cloning. “I’m not advocating that we go out and clone people,” Jirtle said in a phone interview, joking that he has two children made “the old-fashioned way.”

Jirtle’s journey extends back a decade, to early research on imprinted genes. One of the first discovered was a receptor for insulinlike growth factor II (IGF2R). In 1991, Denise Barlow, PhD, then at the Research Institute for Molecular Pathology, Vienna, Austria, reported that IGF2R was imprinted in...
mice (Nature. 1991;349:84-87). Researchers then went on to make knockout mice lacking IGF2R. Like children with Beckwith-Wiedemann syndrome, the mice displayed traits eerily similar to those now being seen in LOS clones. “They grow about 50% larger; they’re structurally abnormal,” said Jirtle. “The lungs just don’t develop. The heart becomes massive so you have cardiovascular problems.” It appeared that insufficient IGF2R led to an excess of available insulinnlike growth factor II, which led to excessive growth.

In people, insufficient IGF2R often leads to cancer. A radiation oncologist by training, Jirtle delved into imprinting during his research on IGF2R’s role as a tumor suppressor gene. “I had no idea what it was,” he said. But as he learned more, he devoted more and more time and laboratory space to the effort. Today, he runs a 40-person laboratory outfitted exclusively for imprinting research.

CONFLICTING REPORTS
As Jirtle’s interest grew, so did a debate about IGF2R. In mice, there was no question that it was imprinted. But in people, there were conflicting reports, which Jirtle said stemmed from problems with the use of the new and unfamiliar laboratory methods being developed. A few articles reported that IGF2R was imprinted in perhaps 50% of the population. “That was very problematic,” said Jirtle. “If a lot of people were imprinted, you would predict them to be exquisitely susceptible to tumor formation.”

So he directed his laboratory to help resolve the debate. Using techniques springing from the Human Genome Project, the team found no evidence of imprinting in various tissues from 75 human fetuses and 12 full-term placentas (Hum Mol Genet. 2001;10:1721-1728). Because every other imprinted gene found in the mouse was also imprinted in humans, Jirtle’s interest peaked. He wanted to know at what point the species diverged.

After collecting tissue samples from a Noah’s Ark of mammals and birds, he and his team concluded that IGF2R imprinting first appeared about 175 million years ago, when live-bearing mammals split from egg layers on the evolutionary tree. Just three of these monotrems exist today, the platypus and two species of spiny anteater. The platypus, at least, does not carry the imprinted gene, a result that helped resolve one of the biggest debates in mammalian evolution (Mamm Genome. 2001;12:513-517).

Drawing on help from Andrew Hoffman, PhD, of Stanford University School of Medicine, and with tissue from the Duke University Primate Center, Jirtle then showed that opossums, pigs, cows, sheep, rats, and mice did carry the imprinted version, but primates did not. From the most primitive prosimian, the colugo, through tree shrews, lemurs, and people, he found no evidence of imprinting. “Mother nature took care of this overgrowth problem 70 million years ago,” said Jirtle, when primates split from other mammals.

Why? Jirtle’s pet theory is that primates mothers ran into a fetal overgrowth problem. As animals got smarter and brains became larger, pelvises stayed the same size. “If you look at humans,” he said, “we’re very close to not being able to deliver. Dying during childbirth was common until recently.” In early human ancestors, then, fetuses that lost the imprinting, perhaps through some epigenetic mutation, would have had twice as much IGF2R as normal, preventing overgrowth. More of those that kept the imprint would perish during birth. Natural selection would take care of the rest. “There’s no way to prove it,” said Jirtle with a chuckle. His current research is comparing snippets of platypus and opossum DNA in a quest to find out why opossums, the most primitive live-bearing mammals, carry the imprint, while platypuses do not. He speculates that imprinting allowed live birth to become a viable evolutionary strategy.

He is also convinced that the lack of IGF2R imprinting in people decreases the odds of LOS during cloning. Support comes from an article Wilmuth published earlier this year (Nat Genet. 2001;27:153-154). It showed that reduction in IGF2R leads to LOS in sheep fetuses. That reduction stems directly from epigenetic errors and imprinting defects that occur during embryo culturing. Wilmuth concluded that his study shows a “causative role for IGF2R loss in sheep.”

TROUBLED RESEARCHERS
While Jirtle is confident in his interpretation of the data, his announcement to the media disturbed both Wilmuth and Rudolf Jaenisch, PhD, of the Whitehead Institute at the Massachusetts Institute of Technology. Jaenisch said in a phone interview, “He argues that this is a key gene for cloning. That is nonsense, it’s not a key gene.”

In his many mouse cloning experiments, Jaenisch said he has not seen any problems with IGF2R. Earlier, at the National Academy of Sciences cloning workshop, Jaenisch implored the panel to recognize that it is foolhardy to “focus on gene imprinting. It’s part of the problem but not all of it.” He said that preliminary evidence from his laboratory showed faulty regulation of non-imprinted genes in clones as well. Jaenisch also disputes the claim that IGF2R has been proven to cause LOS. He wants much more evidence.

Jirtle agreed that there could be other problems that lead to overgrowth. But he thinks the chances are slim. “If you look at the [IGF2R] knockout animals, it’s incredible. If you look at the clones, it’s incredible. They’re absolutely identical” in overgrowth traits, he said.

While debate on scientific points like this will continue, and while research on epigenetic problems in cloning will steam ahead, Jaenisch said he was angered by what he sees as Jirtle’s manipulation of the media. He’s worried that those who want to clone humans—people he calls “nuts”—will point to Jirtle’s research and say that it gives them the green light.

Jirtle’s response: “It doesn’t mean we’re at green, but we’re not at red either. We’re at amber.”
Gene Mutation Link With HIV Resistance

Joan Stephenson, PhD

People who inherit only one copy of a mutated gene that has an effect on HIV's ability to enter CD4 T-helper cells appear to be substantially less likely to become infected with the virus, according to a new report by researchers at New York University School of Medicine in New York City and collaborators at other institutions.

Such a protective effect, if proven, falls far short of completely safeguarding individuals who carry a single copy of the gene mutation from the risk of HIV infection. But, if the study's findings are validated, they suggest that drugs under development that are designed to mimic the mutation's effects need not work perfectly in order to offer a meaningful degree of protection.

**Mutation Mechanism**

The gene under study encodes a cell surface receptor called CCR5 that HIV-1 usually requires (in addition to the CD4 receptor) to invade CD4+ T cells. Scientists have long been aware that a mutation called CCR5-Δ32 results in a faulty receptor, and that people who inherit two copies of the mutated gene (and, thus, have no working CCR5 receptors) are highly resistant to HIV infection.

Prior research had also established that HIV disease also progresses more slowly in individuals who inherit one copy of a gene with the “delta-32 mutation.” But researchers have been uncertain whether such individuals would also have some protection against becoming infected.

Now, however, investigators conducting a multicenter prospective cohort study of nearly 3000 HIV-seronegative individuals considered at high risk for becoming infected with the virus have found that having only one copy of the mutated gene may reduce the risk of HIV infection by 70%. The new findings were published in the August 15 issue of the *Journal of Acquired Immune Deficiency Syndromes*.

About 1% of whites have two genes with the delta Δ32 mutation, which is comparatively rare in nonwhites.

The researchers reasoned that if the Δ32 mutation reduces a person's susceptibility to HIV infection, there would be an increased prevalence of this mutation among uninfected individuals with histories of longer or more intensive exposure to HIV compared with those without such histories. To explore this possibility, they determined the prevalence of the Δ32 mutation among the 2996 HIV-negative study participants, a group comprising men who have sex with men (MSMs), male injection drug users (IDUs), women at heterosexual risk of HIV infection, and female IDUs.

**Part of HIVNET Study**

Study participants were part of a larger research effort, the HIVNET Vaccine Preparedness Study, which enrolled 4892 HIV-negative high-risk individuals in seven US cities. The follow-up rate was 88% at 18 months.

The researchers interviewed participants about risk behaviors and tested them for HIV every 6 months for 18 months (for men) or 24 months (for women).

The final results did not include information about female participants because there were too few enrolled in the study for results to be statistically significant, noted Michael Marmor, MD, who led the work.

Some 1.3% of study participants had two copies of the gene with the mutation, and 12.9% had one. The investigators found (after adjusting for potential confounding associated with recent risk behaviors, including unprotected receptive anal sex) that during the 18-month follow-up period, men who carried one copy of the gene with the Δ32 mutation were 70% less likely to become infected compared with men who lacked the mutation.

Such a protective effect against infection “would be expected if individuals with this genotype have lower numbers of CCR5+ CD4+ T cells or reduced CCR5 expression,” they said.

The study’s findings also confirmed that men with two copies of the mutated gene appear to have substantial protection against infection compared with men with one or no copies—an effect most apparent among older MSMs living in cities with a high HIV prevalence. Although only 1% of the white population has a genetic makeup that includes two copies of the Δ32 gene mutation, nearly 11% of white gay men aged 45 or older who lived in San Francisco and New York City and were HIV negative when the study began in 1995 had two copies of the mutated gene, compared with 0.6% of men aged 18-29, 1.2% of men aged 30-34, and 4.7% of men aged 35-44.

“Strong natural selection pressures, probably unmatched in more recent times in the United States, were exerted on MSM populations, and it is not surprising that a substantial fraction of MSM who remained HIV-seronegative despite continued practice of anal intercourse should possess genetic resistance to infection with the most prevalent HIV strain,” the researchers said.

However, even individuals with two copies of the mutated gene are not completely protected against HIV infec-
tion, because some strains of HIV use other coreceptors to infect cells. Tests revealed that the only person with this genetic makeup who became infected with HIV during the study had a strain of HIV that used CXCR4 receptors.

MAY AID VACCINE EFFORT

Vaccine researchers may want to take the new findings into account when conducting vaccine trials, noted Marmor. “There may be subsets of gay men in cities such as New York or San Francisco where the prevalence of persons with resistance to HIV might be fairly high,” he said. It may be useful to take CCR5 mutation status into consideration when designing studies or analyzing data from vaccine trials.

The new finding, if validated in other studies, also provides some encouragement for researchers who are working on possible anti-HIV drugs aimed at blocking the CCR5 receptor, said Marmor. “The study suggests that strategies for blocking CCR5 receptors may have utility for reducing [HIV] transmission, and if so it might not be necessary to block all of the receptors to obtain some protection,” he said. “Reducing the number of receptor sites per cell may be adequate to provide an imperfect but important degree of protection.”

MISCELLANEA MEDICA

- Lloyd E. Ratner, MD, has been named director of the transplantation division in the Department of Surgery at Thomas Jefferson University Hospital, Philadelphia, Pa. He was formerly director of renal transplantation and associate professor of surgery and pathology at Johns Hopkins University School of Medicine.
- Jorge Carlos Rios, MD, has been named executive dean of Ross University School of Medicine in Portsmouth, Dominica. He was formerly at the Center for Drug Evaluation and Research of the US Food and Drug Administration.
- Robert Kay, MD, chief of staff at Cleveland Clinic in Ohio, has been elected chair of the board of directors of the American Medical Group Association, an organization representing 300 multispecialty medical group members.
- Six health professionals have been named Robert Wood Johnson Health Policy Fellows for 2001-2002 by the Institute of Medicine. They are: Doug Campos-Outcalt, MD, MPA, medical director, Maricopa County Department of Public Health, Phoenix, Ariz; Howard P. Forman, MD, MBA, associate professor of radiology and management and vice chair, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Conn; Suzanne Bennett Johnson, PhD, professor and director, Center for Pediatric Psychology and Family Studies, University of Florida Health Science Center, Gainesville; Louis A. Kazal, Jr, MD, chief medical officer, Navajo Health Foundation, Sage Memorial Hospital, Ganado, Ariz; Andrew G. Kumpuris, MD, private physician, St Vincent’s Hospital, Little Rock, Ark; and Scott S. Young, MD, executive vice president, Utah Health Care Institute, Midvale.
- Mary Jo Gorman, MD, has been named vice president of medical affairs at IPC–The Hospitalist Company, headquartered in North Hollywood, Calif. She had been the company’s regional medical director, based in St Louis, Mo.
- James A. Zimble, MD, a retired vice admiral and former surgeon general of the US Navy and current president of the Uniformed Services University of the Health Sciences, Bethesda, Md, has been awarded the 2001 Frank Brown Berry Prize in Federal Health.
- Albert B. Deisseroth, MD, PhD, has been named president and chief executive officer of the Sidney Kimmel Cancer Center in San Diego, Calif. He was formerly at Yale University School of Medicine, New Haven, Conn, where he was director of the Genetic Therapy Program, chief of the Section of Medical Oncology, and associate director for clinical research of the Yale Cancer Center.
- Aaron Gilbert, MD, has been appointed medical director of the Inpatient Orthopaedic Rehabilitation Program at the Rehabilitation Institute of Chicago. Also at the RIC, Serena Satcher, MD, is the new medical director of the 5-South Inpatient Rehabilitation Unit, and Todd Kuiken, MD, PhD, has been named director of physician fellowships for the RIC/Northwestern University Department of Physical Medicine and Rehabilitation.
- Michael J. Vergare, MD, the Daniel Lieberman Professor and chair of the Department of Psychiatry and Human Behavior at Jefferson Medical College of Thomas Jefferson University, and medical director of the Jefferson Behavioral Health Network, in Philadelphia, Pa, has received the Judicare 2001 Medical Services Award. The award is given to medical professionals for outstanding contributions to the medical care of older Philadelphians.
- Joseph Geradts, MD, has been appointed to the faculty of the Department of Pathology and Laboratory Medicine at Roswell Park Cancer Institute, Buffalo, NY. He was formerly at the Nuffield Department of Clinical Laboratory Sciences, University of Oxford and John Radcliffe Hospital, Oxford, England.
- John M. Ham, MD, has become director of the liver transplantation program at Oregon Health and Science University–Portland Veterans Affairs Medical Center in Portland. He was director of the Living-Donor Liver Transplant Program and the Pancreas Transplant Program at Virginia Commonwealth University and McGuire Veterans Administration Medical Center in Richmond.

Editor’s Note: Miscellanea Medica appears in the Medical News & Perspectives section occasionally. Items submitted for consideration should be directed to the attention of Marsha F. Goldsmith, Editor, Medical News & Perspectives.

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