FOIA Number: 2006-0462-F

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8TH STORY of Level 1 printed in FULL format.

Newsweek

March 10, 1997 , UNITED STATES EDITION

SECTION: SOCIETY; Pg. 52

LENGTH: 3579 words

HEADLINE: Little Lamb, Who Made Thee?

BYLINE: BY SHARON BEGLEY, With STRYKER McGUIRE in Edinburgh, ANNE UNDERWOOD and ADAM ROGERS in New York and MARY HAGER in Washington

HIGHLIGHT:
Dolly's was the birth heard round the world. The first mammal ever cloned from a single adult cell, she was living proof that scientists had solved one of the most challenging problems of cell biology. Her creation raised a troubling question: can humans, too, be cloned?

BODY:

KEITH CAMPBELL WASN'T THINKING, REALLY, ABOUT ROOMS full of human clones, silently growing spare parts for the person from whom they had been copied. Nor was he thinking about giving lesbians a way to bear a biological descendant without visiting the sperm bank. And he certainly wasn't aiming to give pro-team owners a tool to copy their greatest players, hospitals their best doctors or parents their dying child. Campbell, a cell biologist at the Roslin Institute in Scotland, was thinking . . . sheep. Lots of sheep, hillock upon hillock of sheep, enough sheep (given enough fences) to put all the insomniacs in Scotland to sleep. And all produced from a single cell of a single ewe.

Cloned.

Campbell knew that cloning from an adult mammal was, according to every textbook, impossible. He knew that once a cell has decided what it's going to be when it grows up -- part of bone, nerve, skin or any other organ -- it is like a CD album that will play only a single track. Although every cell in every body, from liver cells in a person to udder cells in a sheep, contains the complete genetic blueprint for making the entire person or the entire sheep, only the genetic melody for the liver cell or the udder cell is actually played. The other tracks -- instructions for the complete organism -- have been silenced. But Campbell would have none of that. He and his Roslin colleagues were going to clone a lamb from an adult cell. Even though everyone said it couldn't be done.

At Roslin they stopped saying that in February 1995, after Campbell strode down the hall to the professorially messy office of his colleague Ian Wilmut. He had figured out, he told Wilmut, how to get adult cells to sound each and every one of the genetic notes required to make a complete animal. The key was to make the cell "quiescent," or inactive. In that state, all of its genes have the potential of being played, Campbell realized. All that was needed was the player. And Campbell had just the thing: a sheep oocyte -- egg cell -- contains special proteins that turn on genes, playing all the tracks, one after another, like the laser beam in a CD player. "We have to be very quiet about it," Campbell told Wilmut. "We can't tell anybody." And he didn't, until last week, when the world learned of the arrival of Dolly, born last July, the first

mammal cloned from an adult cell.

Cloning -- manipulating a cell from an animal so that it grows into an exact duplicate of that animal -- is the forbidden fruit of biotechnology. Some scientists were so sure it could not be done that, in the 1970s, they dissuaded bioethicists from pondering its moral implications. Yet at the same time other scientists, in out-of-the-way labs and under the cloak of secrecy, were getting ever closer to making clones. What cloning is not, despite all the professions of surprise in the wake of Dolly's birth announcement last week, is unexpected. For 10 years scientists have been cloning sheep and cows from embryo, though not adult, cells. And the research hasn't stopped with the beasts of the field. In 1993, embryologists at George Washington University cloned human embryos: they took cells from 17 human embryos (defective ones that an infertility clinic was going to discard), all two to eight cells in size. They teased apart the cells, grew each one in a lab dish and got a few 32-cell embryos -- a size that could be implanted in a woman (though they weren't). So scientists' professed surprise over Dolly rings somewhat hollow.

The real question, of course, was, wherever the lamb went, was Mary sure to follow? In other words, how soon will scientists clone humans? Nature, the scientific journal that published the Dolly paper, editorialized, "Cloning humans from adults' tissues is likely to be achievable any time from one to ten years from now." Cornell University biologist W. Bruce Currie estimates that only 10 labs in the world (his not among them) can manipulate sheep cells the way Dolly's makers did, getting them to become quiescent and producing clones from them. But in principle "there is no difficulty at all in driving human cells [in a lab dish] into [quiescence]," says Currie. "All that's needed is to take a culture of proliferating cells and deprive them of [nutrients]." Last week, as scientists cast about, almost desperately, for an obstacle to human cloning, embryologist Colin Stewart of the National Cancer Institute came up with one. In sheep embryos, the genes from the donor cell do not turn on until the egg has divided three or four times, he pointed out. In humans, those genes turn on after two divisions. That difference might be an insurmountable obstacle to human cloning -- or it might not. But on the more profound question of what, exactly, a human clone would be, doubters and believers are unanimous. A human clone might resemble, superficially, the individual from whom it was made. But it would differ dramatically in the traits that define an individual -- personality and character, intelligence and talents. "Here's the rule," says psychologist Jerome Kagan of Harvard. "You will never get 100 percent identity -- never -- because of chance factors and because environments are never exactly the same."

That was small comfort to politicians, ethicists and pundits. President Clinton, citing "serious ethical questions," ordered a federal bioethics panel to report in 90 days on whether the United States should regulate human cloning or ban it. (Britain, Denmark, Germany, Belgium, the Netherlands and Spain already do.) Ethicists dusted off arguments they had mothballed in the 1970s, and thousands of trees gave their lives so dueling scholars could publish articles arguing that cloning was a humane way for infertile couples to have a child, joking that cloning made males superfluous or conjuring hideous images of cloned humans raised for spare parts.

That prospect seems awfully remote from the Roslin Institute's mundane goal: building a better glass of milk. The scientists, backed by PPL Therapeutics P.L.C. of Edinburgh, wanted to genetically engineer sheep and cows so that

their milk contains human proteins. Not just any proteins, but those with pharmacological uses -- medicines. Earlier this year PPL threw a coming-out party for Rosie, a cow whose milk contains human alpha-lactalbumin. This protein contains just about all the amino acids a newborn needs; the idea is to purify the protein from Rosie's milk and sell it, in powdered form, for premature babies who cannot nurse. Other companies are also banking on animals with human traits, for everything from blood to hearts.

ROSIE MAKES A HUMAN protein because, when she was a mere embryo in a dish, scientists slipped the gene for the protein into her cells. (The human gene is rigged so that the protein is made only in milk glands and not in, say, the retina.) When Rosie was born she carried the human gene; this makes her a "transgenic" animal. But putting a human gene into each and every Rosie-to-be is not only tedious but inefficient. It fails more often than it succeeds. Wilmut figured that cloning offered a better way. His recipe: first make transgenic sheep, which he preferred to cows. When the lamb grows up, take one of its cells, slip it into an egg cell from a different sheep, put the whole package into a surrogate mother sheep and wait 150 days. Do this a few times and pretty soon there is a flock of sheep making medicine-laced milk. After he built up a flock of maybe 10 cloned sheep, Wilmut figured, he would breed the animals the old-fashioned way. That way the flock would be more genetically diverse and thus less vulnerable to viruses and disease.

The stumbling block to cloning had been that cells in an adult animal have already chosen what they want to be when they grow up. They are liver cells, or skin cells, or neurons, for instance. Any gene not needed in a cell is switched off, though still present. As a result, skin cells do not make estrogen; brain cells do not make insulin. Proteins, acting like a medieval chastity belt, seem to block a cell's access to those genes. For this reason scientists had never cloned an adult cell: like a frustrated knight, they couldn't get at all the genes needed to make a complete animal.

The Scottish scientists' key discovery was making adult cells live up to their full potential. First the researchers removed udder cells from a 6-year-old pregnant sheep. They grew the cells in lab dishes, immersing them in nutrients. Then, in the eureka step that sent Campbell down the hall to Wilmut two years ago, they dialed back the nutrients to one twentieth of what cells need to grow. After five days the cells had become quiescent, stilled at exactly that stage in their life cycle when their genes are open to what the Roslin scientists call "reprogramming of gene expression." In other words, the genes could receive signals from the ovum that they should start making a lamb embryo. It is hardly a foolproof method -- of 277 adult cells fused with ova, only 13 pregnancies resulted and only Dolly was born alive -- but it is better than anyone else has ever done.

The Roslin scientists had no sooner trotted out Dolly than they assured everyone who asked that no one would ever, ever, apply the technology that made Dolly to humans. Pressed to answer whether human cloning was next, scientists prattled on about how immoral, illegal and pointless such a step would be. But as The Guardian of London pointed out, "Pointless, unethical and illegal things happen every day." If society decided that it wanted to stuff the cloning genie back into the bottle, could it? In the case of nuclear bombs, the five nuclear powers have controlled proliferation, more or less, in part because the United States showed, at Hiroshima and Nagasaki, what horrors the bomb can wreak. The taboo on biological weapons has also held. And with the exceptions of the

Iran-Iraq War of the 1980s and the Tokyo subway attack by the Aum Shinrikyo cult in 1995, chemical weapons, too, have remained on the shelf, at least since the horrific mustard-gas attacks of World War I. Will it take a few human-clone disasters to bring a ban?

Technologies that require big capital investments and infrastructure, like weapons, are easier to control than those that can be carried out by a couple of graduate students in a basement lab. The United States, for instance, bans the use of government money for research on human embryos. But in January a biologist at George Washington University resigned after he was discovered doing research on human embryos in an attempt to find a way to diagnose those with genetic abnormalities. It is easy to imagine another researcher, also with altruistic motives, attempting to clone humans despite a ban. It is equally easy to imagine creepier reasons for cloning. The journal Nature reported that, just before its Dolly issue went to press, it received an e-mail from a Harvard University scholar, pleading that the paper be dropped because "abuse [of the cloning technique] by extralegal or foreign groups is almost inevitable." Alarmism? British futurologist and author Patrick Dixon claimed last week that he had been contacted by a woman who wanted to clone her deceased father -- and possibly carry the baby to term herself.

But who, exactly, would that baby be? Both the dreams and the nightmares of cloning -- the thousands of Mother Teresas and the thousands of Pol Pots -- are no closer to reality after Dolly than they were before. As far as anyone can tell, Dolly is an exact copy of the ewe whose DNA she carries. But with sheep it's kind of hard to spot differences anyway. When it comes to people, genes are only the start, as even Hollywood recognized 19 years ago. In "The Boys From Brazil," the 94 boys made from one of Hitler's cells were exposed to the same traumatic and other formative experiences as Hitler, for the fictional plotters knew that genes alone would not guarantee Fuhrers II through VC.

If Dolly had been born 10 years ago, the explanations would have ended there, with comforting boilerplate about how people are more than their genes, how they are complex products of their interactions with their parents, their friends, their teachers, their culture and their times. But Dolly happened along just when behavioral geneticists and psychologists have begun to figure out exactly how genes -- nature -- are either turned up or turned down by their environment -- nurture. "Environmental influences can alter the physical structure of the brain, determining in part how genes express themselves in both biology and behavior," notes psychiatrist Stanley Greenspan of George Washington University in his new book "The Growth of the Mind."

Take shyness, considered the most heritable personality trait. Harvard's Kagan has found that foetuses with fast heartbeats tend to become shy babies. In other words, these children are biologically predisposed to be supercautious and anxious. (The genes seem to have something to do with making the brain recoil from stimulation and new experiences.) But if parents nudge their shy children into situations that they would otherwise cringe from, like playing with other kids, the biochemical systems that induced shyness in the first place may somehow get dialed back. Which leads to lesson one for would-be cloners: if you clone a sociable person but then protect the precious creation with the zeal of Juliet's nurse, you may produce a quaking wallflower.

Achievement is under even weaker genetic control. "A Mozart born into a primitive tribe in Papua New Guinea would never have written a symphony," says

neurologist Harold Klawans of Rush Medical College in Chicago. But because Mozart's father was a composer and his older sister took piano lessons, whatever innate talent little Wolfgang possessed could be realized. Intellectual revolutionaries are also made and not born, let alone cloned. Frank Sulloway of MIT, who has made his reputation with studies showing how birth order influences everything from political views to personality, argues that "if Darwin had been his mother's firstborn, he would not have been an evolutionist." Based on data from 600 of Darwin's contemporaries, Sulloway calculates that only 5 percent of (conformist) firstborns were evolutionists, but 50 percent of (establishment-challenging) later-borns were. Moreover, Darwin came from a politically and religiously liberal family. "He's loaded to the gills with everything that could have made someone a revolutionary," says Sulloway. Lesson two: to clone an iconoclast, make him your second child.

Which is not to say that genes do not matter. They do. Genes gently nudge a baby into certain behaviors, which then shape her world by, among other things, eliciting from those around her certain kinds of reactions. But the reactions, and the baby's experiences, are hardly predestined and outside human control. Yes, a squalling baby can make his parents angry, even abusive; but parents can recognize the destructive cycle that's beckoning and make a herculean effort to hug, kiss, hold, talk to and coo at him. And the baby "genetically predestined" to be emotionally cold may become a loving preschooler. Conversely, parents who give in to the oversensitive baby, letting her play alone, only exacerbate innate tendencies; parents who withdraw from the difficult baby exaggerate his worst traits. Parents, says Greenspan, can "change the way their [children's] nervous systems work and thus their personalities." Lesson three: genetic seldom means immutable.

EVEN PHYSICAL TRAITS, such as risk for a disease, can be pumped up, damped down or even snuffed out by life's experiences. About 15 percent of women who inherit BRCA1, known as the breast-cancer gene, do not get the disease. Something in their environment, perhaps dumb luck, protected them. Another gene, related to skin cancer, is turned on by exposure to radiation; if the person carrying the gene takes precautions against ultraviolet rays, he may never get skin cancer, explains Mark Feinberg of Johns Hopkins University. More complex diseases, such as heart disease and mental illness, are even less subject to genetic control. One might clone what seems to be a well-adjusted, healthy person only to find that the clone undergoes experiences that make him hypertensive or schizophrenic. For example, the incidence of schizophrenia doubled among Dutch children born in the Netherlands' "winter of famine" during World War II. Maternal malnutrition can trigger the disease. But a clone of one of these children, a genetic duplicate, might evade schizophrenia if borne by a woman who ate normally during pregnancy. Lesson four: don't count on avoiding a genetic disease just because you clone what seems to be a disease-free person.

What you clone may not be what you get for an even more basic reason: the cell being cloned has undergone years of mutations. These changes in its genes -- caused by radiation, chemicals or just chance -- might not have caused any apparent problem. If a gene for a brain chemical is mutated in a skin cell, it's not even detectable. But what if a lab happened to be unlucky enough to choose that cell to clone? The baby would be born with horrible or even fatal defects. "[Mutations are] a problem with every cell, and you don't even know where to check for them," says reproductive biologist Ralph Brinster of the University of Pennsylvania. Aging also affects the cloned cell, and perhaps the animal grown from it. Although Dolly looks like an 8-month-old lamb (albeit a pudgy one,

because her handlers have to keep feeding her to make her stand still for photographers), is she, biochemically, really 6 years old, the age of the ewe from whose cell she came?

If Dolly's creation offers any lessons, it is these. First, that which is not absolutely prohibited by the laws of nature is possible. Second, science, for better or worse, almost always wins; ethical qualms may throw some roadblocks in its path, or affect how widespread a technique becomes, but rarely is moral queasiness a match for the onslaught of science. Society, then, would do well to face the fact that no known law of nature prohibits the cloning of humans. If it wants a voice in whether adults clone themselves, either to raise as children or to grow spare parts, the time to speak up is now.

Or maybe we shouldn't worry about it. After all, they say it won't be done.

Reproductive Rites
Technologies for reproduction started small, on the farm, but embryology and genetics moved them from animals to humans to clones. The progress has been steady -- both in science and science fiction.

1950
First successful freezing (at -79 degrees C) of bull semen for transport and later insemination of cows

1952
The first animal cloning: Robert Briggs and Thomas King make frogs from tadpole cells

1962
John Gurdon also clones frogs, this time using cells from older tadpoles

1978
The film 'The Boys From Brazil' posits a plot to clone little Hitlers

1978
The birth of Baby Louise, the first child conceived through in vitro fertilization. Midwives: Patrick Steptoe and R. G. Edwards of England.

1978
David Rorvik's book 'In His Image' alleges a human cloning

1983
First human mother-to-mother embryo transfer

1985
Ralph Brinster's lab creates the first transgenic livestock, pigs that produce human growth hormone

1986
Artificially inseminated, surrogate mother Mary Beth Whitehead carries Baby M to full term, then tries to keep her. She fails.

1993
* 'The X-Files' episode 'Eve' features psychotic clones
* Human embryos cloned

* 'Jurassic Park's' cloned dinosaurs fill theaters

1994-96
Marvel Comics runs confusing 'Spider-Man' clone saga, in which our hero is thought to be a clone, but turns out just to be a superhero

1996
* Michael Keaton clones himself in 'Multiplicity'
* Wilmut and colleagues announce birth of sheep cloned from embryonic cells, presaging Dolly

Send in the Clones
Scientists once thought that cloning an animal from an adult cell was impossible. Although every cell contains the complete genetic blueprint for making a new animal, those instructions cannot be read in adult cells; they've become specialists, producing cells only for a single body part. The Scottish team figured out how to turn on all the genes needed to make a lamb from a single adult sheep cell.

1 A Finn Dorset ewe provides the mammary cell for cloning.

2 A mammary cell contains copies of every gene needed to make a sheep, but only genes for proteins required by mammary cells are active.

3 Cells grow and divide, making carbon copies of themselves. But if the cells are starved of nutrients, they enter a quiescent state. At this point all of their genes can be activated.

4 A Scottish Blackface ewe provides the egg.

5 The egg, or oocyte, is kept alive in a laboratory dish.

6 The nucleus is removed from the egg.

7 The mammary cell and the egg fuse with a spark of electricity. Molecules in the egg then program genes in the mammary cell to produce the lamb embryo.

8 Clusters of embryonic cells are grown.

9 Embryos are implanted into a surrogate mother.

10 The lamb that results is a clone of the donor ewe.

GRAPHIC: Cover Photo Illustration, no caption, by Tom Haynes. Computer retouching by David Terban -- Shoot Digital.; Picture 1, THE COVER: Dolly's birth was heard round the world. The first mammal ever cloned from a single adult cell, she raised a troubling question: can humans be cloned, too? A look at the science -- and the ethics.; Picture 2, Derived from mammary cells, she surely made her namesake, Dolly Parton, proud; Pictures 1 and 2 by CHRIS BUCK; Picture 3, Dr. Ian Wilmut, in his Roslin Institute lab, was just looking to build a better glass of milk -- containing medicine for premature babies, NAJLAH FEANNY -- SABA; Pictures 4 through 14, no caption, DAN MCCOY -- RAINBOW, JEAN CLAUDE REVY -- PHOTOTAKE, ROBIN SMITH -- TONY STONE IMAGES, EVERETT COLLECTION, REX USA, COURTESY AMERICAN RED CROSS -- VIRGINIA POLYTECHNIC INSTITUTE, RICKI ROSEN -- SABA, KOBAL COLLECTION, (c) MARVEL ENT. GROUP; Picture 15, The key

was getting a single cell to grow into an entire sheep. Above, an embryo cell before manipulation. REPRINTED BY PERMISSION FROM NATURE, VOL. 385, 1997; Diagram, no caption, BLUMRICH -- NEWSWEEK; Pictures 16 and 17, It's All Happening at the Zoo, Cloning might be one way to protect endangered species, but zoos are using other reproductive methods. At the Louisville Zoo, a surrogate mother horse gave birth to a zebra that had been conceived in a lab dish. Last year the world's first test-tube gorilla, Timu, was born at the Cincinnati Zoo. SYGMA, (c) CINCINNATI ZOO

LANGUAGE: ENGLISH

LOAD-DATE: March 11, 1997

16TH STORY of Level 1 printed in FULL format.

Time

March 10, 1997

SECTION: SPECIAL REPORT; MONEY IN MOTION; Pg. 72

LENGTH: 551 words

HEADLINE: BEARISH ON BIOTECH ;
LAYMEN SHOULD STAY AWAY LEST THEY GET FLEECED

BYLINE: DANIEL KADLEC

BODY:

Dormant for years, the biotech bug is once again infesting stocks. This nasty man-made microbe, hatched in the labs of Wall Street, surfaces every few years to prey on susceptible (i.e., gullible) investors. Symptoms include feverish optimism followed by cold chills of reality.

The cyclical critter was due to hatch again anyway, but last week's revelation that Scottish scientists had succeeded in cloning a sheep amounted to a final whack at the snooze button. Now investors are wide awake to the potential wonders of biotechnology for the first time since a euphoric rally in those stocks in 1991. If you're a doctor or scientist, go ahead and take your best shot. Biotech certainly holds great promise, and you may well understand enough to pick the few stocks that will thrive. But overall the industry has been so consistently disappointing that laymen should stay away lest they get fleeced.

Consider that of the 300 or so publicly traded U.S. biotech firms, only about a dozen stirred up a profit last year. Many are one-drug research outfits in a field where only 1 in 10 drugs gets approved. In many cases, three or four one-note companies are working on the same basic treatment, like wound healing. It's a dicey business.

Recall the Flavr Savr, a tomato bioengineered to ripen on the vine and last months on the shelf. It might have been a huge moneymaker if only the thing had tasted like a tomato. Its maker, Calgene Inc., traded above $ 20 a share in 1992, but the stock subsequently rotted to $ 5, and Monsanto Co. has offered to buy the company for $ 7.25 a share.

That is by no means the most devastating loss stemming from a biotech failure in the '90s. Centocor Inc. fell from $ 60 to $ 5; Xoma Corp., from $ 32 to $ 1; Synergen Inc., from $ 73 to $ 4--all because of hyped septic-shock drugs that didn't work. Inject those babies into your 401(k), and you'll never retire. And these aren't isolated cases. Viren Mehta, a biotech expert at Mehta and Isaly, keeps track of biotech bombs. He says there have been 14 major disasters this decade. But even if you avoid specific product failures, it isn't enough. Biotech stocks fly in swarms. The whole group gets clipped when a few failures surface. In the three years that ended in December 1994, the average biotech stock fell 63%.

The average biotech stock has doubled in two years and reached a four-year high. Following the cloning news out of Scotland, investors indiscriminately

bid up stocks of cloning companies. Shares of PPL Therapeutics of Edinburgh, which helped fund the sheep-cloning research, jumped 16% in a day. There have been some genuine commercial successes, such as Biogen Inc.'s drug Avonex, approved last year to treat multiple sclerosis. Still, a dangerous froth is forming. "During the next six months you're going to see quite a few disasters," predicts Evan Sturza of Sturza's Medical Investment Letter.

There are lots of reasons to root for these companies. High stock prices raise more money to seek important treatments. But after much exposure, I've been able to develop a resistance to the biotech bug. And until the gene-bending gods can separate the hype from the glory, they're not getting any of my savings.

Daniel Kadlec is TIME's Wall Street columnist. Reach him at kadlec@time.com

GRAPHIC: COLOR CHART, HOT AGAIN, American Stock Exchange Biotechnology Index, weekly closings [Chart not available--index illustrated in line graph from 1990 to 1997]

LANGUAGE: ENGLISH

LOAD-DATE: March 3, 1997

10TH STORY of Level 1 printed in FULL format.

Newsweek

March 10, 1997 , UNITED STATES EDITION

SECTION: SOCIETY; Pg. 60

LENGTH: 844 words

HEADLINE: Today the Sheep . . .

BYLINE: BY KENNETH L. WOODWARD, With ANNE UNDERWOOD in New York

HIGHLIGHT:
.. . Tomorrow the shepherd? Before science gets there, ethicists want some hard questions asked and answered.

BODY:
TWENTY YEARS AGO, WHEN only the lowly tadpole had been cloned, bioethicists raised the possibility that scientists might someday advance the technology to include human beings as well. They wanted the issue discussed. But scientists assailed the moralists' concerns as alarmist. Let the research go forward, the scientists argued, because cloning human beings would serve no discernible scientific purpose. Now the cloning of humans is within reach, and society as a whole is caught with its ethical pants down.

Today the sheep -- tomorrow the shepherd? Whether the cloning of human beings can be ethically justified is now firmly, perhaps permanently, on the nation's moral agenda. President Clinton has given an advisory panel of experts just 90 days to come up with proposals for government action. The government could prohibit the cloning of human beings or issue regulations limiting what researchers can do. But the government cannot control the actions of individuals or private groups determined to clone humans for whatever purpose. And science has a way of outdistancing all ethical restraints. "In science, the one rule is that what can be done will be done," warns Rabbi Moses Tendler, professor of medical ethics at Yeshiva University in New York.

Some ethicists regard the cloning of humans as inherently evil, a morally unjustifiable intrusion into human life. Others measure the morality of any act by the intention behind it; still others are concerned primarily with the consequences -- for society as well as for individuals. Father Richard McCormick, a veteran Jesuit ethicist at the University of Notre Dame, represents the hardest line: any cloning of humans is morally repugnant. A person who would want a clone of himself, says McCormick, "is overwhelmingly self-centered. Once Richard McCormick is enough." But why not clone another Einstein? Once you program for producing superior beings, he says, you are into eugenics, "and eugenics of any kind is inherently discriminatory." What's wrong with duplicating a sibling whose bone marrow could save a sick child? That, he believes, is using another human being merely "as a source for replaceable organs." But why shouldn't an infertile couple resort to cloning if that is the only means of having a child? "Infertility is not an absolute evil that justifies doing any and every thing to overcome it," McCormick insists.

Other ethicists see possible exceptions to a general rule against cloning. Tendler opposes cloning on Biblical grounds. But if a sterile

second-generation Holocaust survivor wanted a male heir to continue an otherwise doomed family line, the rabbi says he might advise the man to clone rather than use donor sperm. Boston College moral theologian Lisa Sowhill Cahill is "not yet convinced that cloning human beings is inherently evil." The mother of identical twins, Cahill questions whether creating a clone necessarily violates the dignity of the original or of the genetic copy. As with other ethicists, what most concerns Cahill is the commodification of human beings and their genes. Forget hubris, consider commerce. What's to prevent the transfer of a dollop of DNA to a wealthy bidder who wants an especially beautiful, swift or smart child?

Beyond the arguments of experts, the nation's religious communities "will play an important role in the national debate over cloning," says Quaker ethicist James Childress, a member of the president's advisory panel. All theologians agree that a clone would have a soul like everyone else. Although the pope has yet to address the cloning issue, the Vatican has repeatedly condemned the use of human embryos for nontherapeutic purposes -- which is what cloning requires. Islamic courts have not ruled on cloning, either, but Muslim scholar Abdulaziz Sachedina, a medical ethicist at the University of Virginia, worries about the long-term implications of separating reproduction from human relationships. "Imagine a world with no need for marriage," he asks. Protestant ethicist Allen Verhey of Hope College in Holland, Mich., warns that cloning would program parents to "think of their children as products." And Buddhist scholar Donald Lopez foresees real problems for the theory of karma. Would the clone inherit the karma of the original person? And, he wonders, "what did the sheep do in a previous life that resulting in its being cloned in this one?"

But to judge by what American society currently permits, the nation is already far along the road toward tacit acceptance of cloning. "In our society there are two values which will allow anyone to do whatever she wants in human reproduction," observes ethicist Daniel Callahan of the Hastings Center in Briarcliff Manor, N.Y. "One is the nearly absolute right to reproduce -- or not -- as you see fit. The other is that just about anything goes in the pursuit of improved health." Perhaps the message of Dolly is that society should reconsider its casual ethical slide toward assuming mastery over human life. Do we really want to play God?

GRAPHIC: Picture, Andy Warhol cloning around in 'The Twenty Marilyns', (c) 1997 ANDY WARHOL FOUNDATION FOR THE VISUAL ARTS -- ARS N.Y. -- ART RESOURCE

LANGUAGE: ENGLISH

LOAD-DATE: March 11, 1997

13TH STORY of Level 1 printed in FULL format.

Time

March 10, 1997

SECTION: SPECIAL REPORT; Pg. 62

LENGTH: 1764 words

HEADLINE: THE AGE OF CLONING;
A LINE HAS BEEN CROSSED, AND REPRODUCTIVE BIOLOGY WILL NEVER BE THE SAME FOR PEOPLE OR FOR SHEEP

BYLINE: J. MADELEINE NASH, WITH REPORTING BY HELEN GIBSON/ROSLIN AND DICK THOMPSON/WASHINGTON

BODY:

Even now, a week after news of the achievement first flew around the globe, traces of astonishment linger in the air like a contrail. The landmark paper published late last week in the journal Nature confirmed what the headlines had been screaming for days: researchers at the Roslin Institute near Edinburgh, Scotland, had indeed pulled off what many experts thought might be a scientific impossibility. From a cell in an adult ewe's mammary gland, embryologist Ian Wilmut and his colleagues managed to create a frisky lamb named Dolly (with apologies to Ms. Parton), scoring an advance in reproductive technology as unsettling as it was startling. Unlike offspring produced in the usual fashion, Dolly does not merely take after her biological mother. She is a carbon copy, a laboratory counterfeit so exact that she is in essence her mother's identical twin.

What enabled the Scottish team to succeed where so many others have failed was a trick so ingenious, yet so simple, that any skilled laboratory technician should be able to master it--and therein lies both the beauty and the danger: once Wilmut and his colleagues figured out how to cross that biological barrier, they ensured that others would follow. And although the Roslin researchers had to struggle for more than 10 years to achieve their breakthrough, it took political and religious leaders around the world no time at all to grasp its import: if scientists can clone sheep, they can probably clone people too.

Without question, this exotic form of reproductive engineering could become an extremely useful tool. The ability to clone adult mammals, in particular, opens up myriad exciting possibilities, from propagating endangered animal species to producing replacement organs for transplant patients. Agriculture stands to benefit as well. Dairy farmers, for example, could clone their champion cows, making it possible to produce more milk from smaller herds. Sheep ranchers could do the same with their top lamb and wool producers.

But it's also easy to imagine the technology being misused, and as news from Roslin spread, apocalyptic scenarios proliferated. Journalists wrote seriously about the possibility of virgin births, resurrecting the dead and women giving birth to themselves. On the front page of the New York Times, a cell biologist from Washington University in St. Louis, Missouri, named Ursula Goodenough quipped that if cloning were perfected, "there'd be no need for men."

Scientists have long dreamed of doing what the Roslin team did. After all, if starfish and other invertebrates can practice asexual reproduction, why can't it be extended to the rest of the animal kingdom? In the 1980s, developmental biologists at what is now Allegheny University of the Health Sciences came tantalizingly close. From the red blood cells of an adult frog, they raised a crop of lively tadpoles. These tadpoles were impressive creatures, remembers University of Minnesota cell biologist Robert McKinnell, who followed the work closely. "They swam and ate and developed beautiful eyes and hind limbs," he says. But then, halfway through metamorphosis, they died.

Scientists who have focused their cloning efforts on more forgiving embryonic tissue have met with greater success. A simple approach, called embryo twinning (literally splitting embryos in half), is commonly practiced in the cattle industry. Coaxing surrogate cells to accept foreign DNA is a bit trickier. In 1952 researchers in Pennsylvania successfully cloned a live frog from an embryonic cell. Three decades later, researchers were learning to do the same with such mammals as sheep and calves. "What's new," observes University of Wisconsin animal scientist Neal First, "is not cloning mammals. It's cloning mammals from cells that are not embryonic."

Embryo cells are infinitely easier to work with because they are, in the jargon of cell biologists, largely "undifferentiated." That is, they have not yet undergone the progressive changes that turn cells into skin, muscles, hair, brain and so on. An undifferentiated cell can give rise to all the other cells in the body, say scientists, because it is capable of activating any gene on any chromosome. But as development progresses, differentiation alters the way DNA--the double-stranded molecule that makes up genes--folds up inside the nucleus of a cell. Along with other structural changes, folding helps make vast stretches of DNA inaccessible, ensuring that genes in adult cells do not turn on at the wrong time or in the wrong tissue.

The disadvantage of embryonic cloning is that you don't know what you are getting. With adult-cell cloning, you can wait to see how well an individual turns out before deciding whether to clone it. Cloning also has the potential to make genetic engineering more efficient. Once you produce an animal with a desired trait--a pig with a human immune system, perhaps--you could make as many copies as you want.

In recent years, some scientists have speculated that the changes wrought by differentiation might be irreversible, in which case cloning an adult mammal would be biologically impossible. The birth of Dolly not only proves them wrong but also suggests that the difficulty scientists have had cloning adult cells may have less to do with biology than with technique.

To create Dolly, the Roslin team concentrated on arresting the cell cycle--the series of choreographed steps all cells go through in the process of dividing. In Dolly's case, the cells the scientists wanted to clone came from the udder of a pregnant sheep. To stop them from dividing, researchers starved the cells of nutrients for a week. In response, the cells fell into a slumbering state that resembled deep hibernation.

At this point, Wilmut and his colleagues switched to a mainstream cloning technique known as nuclear transfer. First they removed the nucleus of an unfertilized egg, or oocyte, while leaving the surrounding cytoplasm intact. Then they placed the egg next to the nucleus of a quiescent donor cell and

applied gentle pulses of electricity. These pulses prompted the egg to accept the new nucleus--and all the DNA it contained--as though it were its own. They also triggered a burst of biochemical activity, jump-starting the process of cell division. A week later, the embryo that had already started growing into Dolly was implanted in the uterus of a surrogate ewe.

An inkling that this approach might work, says Wilmut, came from the success his team experienced in producing live lambs from embryonic clones. "Could we do it again with an adult cell?" wondered Wilmut, a reserved, self-deprecating man who likes gardening, hiking in the highlands and drinking good single-malt Scotch (but who was practical enough to file for a patent before he went public).

It was a high-risk project, and in the beginning Wilmut proceeded with great secrecy, limiting his core team to four scientists. His caution proved to be justified; the scientists failed far more often than they succeeded. Out of 277 tries, the researchers eventually produced only 29 embryos that survived longer than six days. Of these, all died before birth except Dolly, whose historic entry into the world was witnessed by a handful of researchers and a veterinarian.

Rumors that something had happened in Roslin, a small village in the green, rolling hills just south of Edinburgh, started circulating in scientific circles a few weeks ago. It was only last week, when the rumors were confirmed and the details of the experiment revealed, that the real excitement erupted. Cell biologists, like everybody else, were struck by the simple boldness of the experiment. But what intrigued them even more was what it suggested about how cells work.

Many scientists had suspected that the key to getting a donor cell and egg to dance together was synchronicity--getting them started on the same foot. Normal eggs and sperm don't have that problem; they come pre-divided, ready to combine. An adult cell, though, with its full complement of genes, has to be coaxed into entering an embryonic state. That is probably what Wilmut did by putting the donor cell to sleep, says Colin Stewart, an embryologist at the National Cancer Institute. Somehow, in ways scientists have yet to understand, this procedure seems to have reprogrammed the DNA of the donor cell. Thus when reawakened by the Roslin team, it was able to orchestrate the production of all the cells needed to make up Dolly's body.

Like most scientists who score major breakthroughs, Wilmut and his colleagues have raised more questions than they have answered. Among the most pressing are questions about Dolly's health. She is seven months old and appears to be perfectly fine, but no one knows if she will develop problems later on. For one thing, it is possible that Dolly may not live as long as other sheep. After all, observes NCI's Stewart, "she came from a six-year-old cell. Will she exhibit signs of aging prematurely?" In addition, as the high rate of spontaneous abortion suggests, cloning sometimes damages DNA. As a result, Dolly could develop any number of diseases that could shorten her life.

Indeed, cloning an adult mammal is still a difficult, cumbersome business--so much so that even agricultural and biomedical applications of the technology could be years away. PPL Therapeutics, the small biotechnical firm based in Edinburgh that provided a third of the funding to create Dolly, has its eye on the pharmaceutical market. Cloning, says PPL's managing director Ron James,

could provide an efficient way of creating flocks of sheep that have been genetically engineered to produce milk laced with valuable enzymes and drugs. Among the pharmaceuticals PPL is looking at is a potential treatment for cystic fibrosis.

Nobody at Roslin or PPL is talking about cloning humans. Even if they were, their procedure is obviously not practical--not as long as dozens of surrogates need to be impregnated for each successful birth. And that is probably a good thing, because it gives the public time to digest the news--and policymakers time to find ways to prevent abuses without blocking scientific progress. If the policymakers succeed, and if their guidelines win international acceptance, it may take a lot longer than the editorial writers and talk-show hosts think before a human clone emerges--even from the shadows of some offshore renegade lab. "How long?" asks PPL's James. "Hopefully, an eternity."

--With reporting by Helen Gibson/Roslin and Dick Thompson/Washington

GRAPHIC: COLOR ILLUSTRATION: ILLUSTRATION FOR TIME BY TIM O'BRIEN, [Drawing of cloned men walking away from gum-ball machine containing additional clones]; COLOR PHOTO: WILLIAM RITCHIE--ROSLIN INSTITUTE, DELICATE OPERATION Researchers at the Roslin Institute use a hair-thin pipette to pierce an egg cell and remove its nucleus and DNA [Magnified image of pipette and egg cell]; FIVE COLOR ILLUSTRATIONS: TIME DIAGRAM BY JOE LERTOLA, [Drawing of Finn Dorset ewe and donor cell; drawing of Blackface ewe and egg cell with DNA highlighted; drawing of donor cell fusing with egg cell; drawing of embryo and Blackface ewe; drawing of Finn Dorset lamb]

LANGUAGE: ENGLISH

LOAD-DATE: March 3, 1997

15TH STORY of Level 1 printed in FULL format.

Time

March 10, 1997

SECTION: SPECIAL REPORT

LENGTH: 64 words

HEADLINE: If you had the chance, would you clone yourself?

BODY:

Yes 7%
No 91%

Is it against God's will to clone human beings?

Yes 74%
No 19%

Should the Federal Government regulate the cloning of animals?

Yes 65%
No 29%

From a telephone poll of 1,005 adult Americans taken for TIME/CNN on Feb. 26-27 by Yankelovich Partners Inc. Sampling error +/- 3.1%. "Not sures" omitted.

LANGUAGE: ENGLISH

LOAD-DATE: March 3, 1997

12TH STORY of Level 1 printed in FULL format.

Time

March 10, 1997

SECTION: SPECIAL REPORT; Pg. 60

LENGTH: 814 words

HEADLINE: A SPECIAL REPORT ON CLONING

BYLINE: CHARLES KRAUTHAMMER

BODY:

One doesn't expect Dr. Frankenstein to show up in wool sweater, baggy parka, soft British accent and the face of a bank clerk. But there in all banal benignity he was: Dr. Ian Wilmut, the first man to create fully formed life from adult body parts since Mary Shelley's mad scientist.

The creator wore chinos. Wilmut may not look the part, but he plays it. He took a cell nucleus from a six-year-old ewe, fashioned from it a perfect twin--adding the nice Frankenstein touch of passing an electric charge through the composite cell to get it growing--and called it Dolly.

Dolly, the clone, is an epochal--a cataclysmic--creature. Not because of the technology that produced it. Transferring nuclei has been done a hundred times. But because of the science. Dolly is living proof that an adult cell can revert to embryonic stage and produce a full new being. This was not supposed to happen.

It doesn't even happen in amphibians, those wondrously regenerative little creatures, some of which can regrow a cut-off limb or tail. Try to grow an organism from a frog cell, and what do you get? You get, to quote biologist Colin Stewart, "embryos rather ignominiously dying (croaking!) around the tadpole stage."

And what hath Wilmut wrought? A fully formed, perfectly healthy mammal--a mammal!--born from a single adult cell. Not since God took Adam's rib and fashioned a helpmate for him has anything so fantastic occurred.

What, then, was the reaction to this breakthrough of biblical proportions?

There is a mischievous story (told mostly in England) that a leading Scottish newspaper reported the Titanic sinking with the headline GLASGOW MAN LOST AT SEA. Well, here was a story that deserved the headline MAN CREATES LIFE. And how does it play? A Wall Street Journal headline urgently asks, WHO WILL CASH IN ON BREAKTHROUGH IN CLONING? (Answer: "Tiny company could emerge a big winner.") The President of the U.S. calls for a committee of experts to gather and pull their beards.

And the New York Times, in a lovely coda to its editorial titled CLONING FOR GOOD OR EVIL, advises that "society will need to sort through what is acceptable and what is the nightmare beyond."

Well, yes. The most portentous scientific achievement since Alamogordo will need a weighing of pros and cons. No kidding.

And, no doubt, the pro-and-con weighing, the pontificating and the chin pulling will now go into high gear. Wilmut will spawn more ethics conclaves than cloned sheep. No matter. There is nothing to stop cloning, not even of humans.

What the politicians do not understand is that Wilmut discovered not so much a technical trick as a new law of nature. We now know that an adult mammalian cell can fire up all the dormant genetic instructions that shut down as it divides and specializes and ages, and thus can become a source of new life.

You can outlaw technique; you cannot repeal biology. And even the outlawing of this technique--Britain, for example, forbids the cloning of humans--will fail. It is too simple, too replicable. No amount of regulation by the FDA or the NIH or even the FBI will stop it.

Why? Not just because it is so easy, but because its potential for good is so immense. The study of cloning can give the world deep insights into such puzzles as spinal cords, heart muscle and brain tissue that won't regenerate after injury, or cancer cells that revert to embryonic stage and multiply uncontrollably. Replicating Wilmut's work will elucidate what he along the way did right that nature, in these pathologies, does wrong.

Of course, the potential for evil is infinitely greater. But there will be no stopping that either. Ban human cloning in America, as in England, and it will develop on some island of Dr. Moreau. The possibilities are as endless as they are ghastly: human hybrids, clone armies, slave hatcheries, "delta" and "epsilon" sub-beings out of Aldous Huxley's Brave New World.

But you don't have to be mad to be tantalized. Being human will do. Think of it: what Dolly--fat, insensible Dolly--promises is not quite a second chance at life (you don't reproduce yourself; you just reproduce a twin) but another soul's chance at your life. Every parent tries to endow his child with the wisdom of his own hard-earned experience. Here is the opportunity to pour all the accumulated learning of your life back into a new you, to raise your exact biological double, to guide your very flesh through a second existence.

Oh, the temptation to know what might have been. Or to produce an Einstein, a Dr. King, for every generation. Or to raise a Jefferson in a clearing, a cross between Jurassic Park and Williamsburg, an artificial environment re-creating 18th century Virginia. Create, nurture and wait. Then bring him out one day, fully grown, to answer the question of the ages: What would Jefferson do today?

--CHARLES KRAUTHAMMER

GRAPHIC: COLOR PHOTO: DIGITAL PHOTOMONTAGE BY ARTHUR HOCHSTEIN. DOLLY, PHOTOGRAPHED FOR TIME BY ROBERT WALLIS--SABA, COVER, Will There Ever Be Another You? A SPECIAL REPORT ON CLONING, [Multiple image of cloned sheep Dolly]; COLOR PHOTO: ROBERT WALLIS--SABA FOR TIME, Good or Baa-ad? Cloning a sheep sets off a worldwide debate on ethics (see SPECIAL REPORT) [Sheep--T of C]; COLOR PHOTO: REUTERS, [Ian Wilmut and sheep]

11TH STORY of Level 1 printed in FULL format.

Time

March 17, 1997

SECTION: SCIENCE; Pg. 60

LENGTH: 1011 words

HEADLINE: NETI AND DITTO;
TWO CUTE NEW CLONES ARE TOO CLOSE FOR COMFORT

BYLINE: CHRISTINE GORMAN

BODY:

It was bad enough when Scottish researchers cloned a sheep named Dolly and commentators started writing about virgin births and Frankenstein. But then one week later, researchers at the Oregon Regional Primate Research Center let it be known that they had cloned a pair of rhesus monkeys, named Neti (for nuclear embryo transfer infant) and Ditto, that squinted in the glare of the TV lights and clung to each other for dear life.

It was two clones too many--or, more to the point, clones too close to human for comfort. Politicians--with one eye on re-election and another on the polls (a TIME/CNN survey reported that 3 out of 4 Americans believe such research is "against the will of God")--wasted no time. The President, proclaiming that "each human life is unique, born of a miracle that reaches beyond laboratory science," banned the use of federal funds for human cloning, while Republican Representative Vernon Ehlers of Michigan introduced not one but two anticloning measures.

Lost in the rush of legislative activity was the fact that Neti and Ditto were not so much a step toward a brave new world as a diversion. They were produced from embryos, which makes them clones only in the way that identical twins or triplets are clones. The same technique has already been used with sheep, cattle, rabbits, pigs and even humans--although in the last case the embryonic clones were destroyed. What makes Dolly special is that she was cloned from an adult sheep, not from an embryo. She is the only mammal ever born that is identical to her biological mother.

She may not be the last, however. As NIH director Dr. Harold Varmus told a congressional subcommittee last week, it could take just one infertile couple, arguing that cloning provides their only chance to bear a child, to turn public opinion around.

--By Christine Gorman

GRAPHIC: COLOR PHOTO: JACK SMITH--AP, LAB MATES: Making monkeys of politicians [Monkeys Neti and Ditto]

LANGUAGE: ENGLISH

79TH STORY of Level 1 printed in FULL format.

BIOWORLD Today

March 31, 1997

SECTION: VOL. 8; No. 61

LENGTH: 732 words

HEADLINE: BIO LETTER TO PRESIDENT CLINTON URGES CAUTION IN CLONING LEGISLATION

BYLINE: Seachrist, Lisa

BODY:

By Lisa Seachrist Washington Editor WASHINGTON While lauding President Clinton's decision to declare a moratorium on research into cloning humans until the National Bioethics Advisory Commission (NBAC) weighs in at the end of May, the Biotechnology Industry Organization (BIO) urged Clinton to oppose hastily drafted legislation that could threaten biotechnology research.In a letter delivered to the president on March 27, BIO recognizes the spiritual and ethical dilemmas raised by the sheep clone, Dolly, but warns that poorly thought out legislation could jeopardize important medical research.

"The board wanted to get on record as having similar concerns to the public," Carl Feldbaum, president of BIO, said. "But we also wanted to state very graphically the risks of bad legislation."

In the letter, BIO notes that Dolly "raises new prospects for which we are not so adequately prepared." And, BIO continues, "these new prospects challenge some of the most fundamental concepts we hold about ourselves as social and spiritual beings."

Nevertheless, the organization points out that cloning the duplication of genes is an essential tool in biotechnology. BIO goes on to say that the cloning of certain human tissues could produce replacement skin, cartilage and bone tissue for burn and accident victims as well as potentially produce cells for cancer therapy. In addition, research into cloning human cells could result in ways to regenerate diseased retinas and severed spinal cords.

"The good news about all of this is that legislators and people in general understand the value of biotech research and they don't want to put it in jeopardy," Feldbaum said. "We just want to make sure that no legitimate research is deterred in the process of creating laws to address human cloning."

BIO said it intends to circulate the letter to both houses of Congress, the NBAC as well as to state legislators in order to educate them about the need for a cautious approach to legislation. "Our position is Let's wait. Let's not jump ahead until we have heard from the president's bioethics commission,'" Feldbaum said.

Already three bills have been introduced in the 105th Congress to prohibit cloning human beings. In the Senate, Christopher Bond (R- Mont.) sponsored S. 368 stating that "no federal funds may be used for research with respect to

the cloning of a human individual." Bond goes on to define the term cloning to mean "the replication of a human individual by the taking of a cell with genetic material and the cultivation of the cell through the egg, embryo, fetal and newborn stages into a new human individual."

Rep. Vernon Ehlers (R-Mich.) introduced two bills in the House. H.R. 922 dictates that "none of the funds made available in any Federal law may be expended to conduct or support any project of research that involves the use of a human somatic cell for the process of producing a human clone." H.R. 923 opens the door to civil penalties for using "a human somatic cell for the process of producing a human clone."

While all of these bills are well meaning, Feldbaum noted that Ehlers' bills leave the door open to interpretations that could stymie biotech research because they don't provide a definition of what is meant by producing a human clone. The Bond bill, while clearer about what is meant by cloning a human, is still under scrutiny, and BIO has not taken a position on it, Feldbaum said.

Even if Congress proceeds cautiously, biotech research faces a threat from state initiatives designed to prohibit human cloning. To date, BIO counts 12 bills that address human cloning in states as varied as Alabama, California and Florida.

"The worst bill is in Florida, where the proposed legislation bans the cloning of human DNA." Feldbaum said that, should such a bill become law, it would effectively eliminate medical research in the state. "This is a bill that we are going to oppose categorically."

"Cloning is not an issue for grandstanding," Feldbaum said. "State legislators need to know that if they enact a poorly written law they could drive biotech and medical research from their state."

The U.S. isn't the only country struggling with the challenge of crafting appropriate legislation. Feldbaum said that he has been informed of a Canadian bill in the Canadian House of Commons that could stymie research in that country.

LANGUAGE: ENGLISH

LOAD-DATE: April 1, 1997

66TH STORY of Level 1 printed in FULL format.

BIOWORLD Today

April 1, 1997

SECTION: VOL. 8; No. 62

LENGTH: 1195 words

HEADLINE: MOVE OVER, YACS; HERE COME THE HACS CASE WESTERNERS CONSTRUCT FIRST ARTIFICIAL HUMAN CHROMOSOMES

BYLINE: Leff, David N.

BODY:

By David N. Leff Science Editor The hourglass-shaped centromere, which pinches the midriff of every human chromosome, carries no genes. Its job is to honcho the proper divvying up of chromosomal DNA during cell division.

"While it's been known since the early years of this century that chromosomes carry genes," said geneticist Huntington Willard, "until now the complexity and size of normal chromosomes has limited our ability to analyze their structure and function."

One of the most complex parts of that overall complexity is the centromere.

"Our successful creation of functional centromeres and incorporation of them into human artificial chromosomes HAC ," Willard observed, "were the critical achievements enabling the stability and normal behavior of the chromosomes during cell division."

Willard, who chairs the department of genetics at Case Western Reserve University, in Cleveland, is senior author of a paper in the April issue of Nature Genetics, titled: "Formation of de novo centromeres and construction of first-generation human artificial chromosomes."

Molecular geneticists have been frustrated in their efforts to create human artificial chromosomes. Instead, they must make do with yeast artificial chromosomes (YAC) in cloning experiments. These are patterned on the genomic DNA of Saccharomyces cerevisiae baker's yeast.

"YACs have been instrumental in allowing the Human Genome Project to move forward," observed cancer biologist John Harrington, the article's lead author. "They've been used to date largely as a cloning vector. Until very recently," he pointed out, "YACs have been the only vector that allowed very large pieces of human DNA to be cloned. By large, I mean from several hundred kilobases up to, and perhaps exceeding, a million bases in size."

Why HACs Lagged Behind YACs

Human chromosomes, which range from about 50 to 250 megabases in size, are 100-fold larger than their yeast-cell counterparts.

"One of the major obstacles confronting people interested in cloning human artificial chromosomes," Harrington told BioWorld Today, "has been an inability to clone a functional human centromere." He counted the reasons why:

"First, it's extremely large, unlike the yeast centromere, which is only 125 base pairs in length.

"Second, the human centromere is made up of extremely repetitive sequences of alpha-satellite DNA. This consists of a 171-base-pair, head-to-tail tandem repeat, iterated over and over again for several thousand base pairs long." Harrington pointed out that "the exact function of this class of DNA is largely unknown, because until now we've never had a system that allowed us to dissect the function associated with these centromeric repeats."

A principal goal of Case Western's two-year HAC-building effort was to provide vectors for gene therapy free of the drawbacks that hamper viral and non-viral DNA vehicles. "Viral vectors," Harrington pointed out, "suffer from serious limitations, such as unstable gene expression, unwanted immune responses, occasional generation of infectious viral particles, and stringent size restrictions, which allow only small genes to be placed in the viral plasmid and delivered to the target tissue."

If genes are the "software" of chromosomes, then their "hardware" consists of the gene-free, wasp-wasted centromere near their middle, and telomeres at each end. The latter are far-out (literally) repetitive regions of DNA, capping both tips of every chromosome. Telomeres act like boundary markers or bumpers to protect the chromosome from unwanted hook-ups, end-to-end, with other chromosomes.

As Harrington recounted, to construct their human artificial chromosomes, he and his co-authors first synthesized arrays of alpha satellite DNA. Then, to this centromeric genetic material, they added telomeres and large fragments of random human genomic DNA. The latter presumably contained origins of replication sequences that regulate the controlled copying of a chromosome's total DNA during cell division. They kick-start the replication process, and thus constitute the business part of a gene-therapy vector.

"This approach," Harrington explained, "simply allowed us, in essence, to make a DNA library within the cells we transfected."

Finally, they inserted this mix into human tumor cell lines. There, like building blocks, these independent elements assembled into miniature versions of human chromosomes.

As for the actual assembly of the HACs inside those cells, Harrington said, "Once we introduced the several DNA ingredients into the cell, they found their way to the nucleus, where they assembled into various HAC combinations. Genes present in both the genomic DNA and in our constructs were then expressed. At 24 to 48 hours after that transfection took place, we put the cells under drug selection, which killed off the vast majority of them.

"Among the survivors," Harrington went on, "were putative human microchromosomes, which persisted inside dividing cells for more than six months of culture. At that point they had all the characteristics of normal human chromosomes, except for size. These HACs are only a tenth as large as native

human chromosomes."

Readying HACs For Gene Therapy Vector Duty

To bring their HACs to the clinic, and to market, three of the paper's co-authors founded Cleveland-based Athersys Inc. in 1994.

Harrington is the company's vice president for research and development. "Athersys was a spin-off of Case Western," he explained, "but is now an independent, privately financed company, which has a very good working relationship with the university."

Geneticist Gil Van Bokkelen is the firm's president and CEO and Willard is a member of its scientific advisory board. All three are inventors on an allowed U.S. patent which, Harrington said, "covers methods of cloning long alpha-satellite DNA sequences up to about 200 kilobases in length, then expanding them in vitro to a megabase long."

Two other patent applications are pending.

Once their prototype synthetic microchromosomes (HACs) are refined for use, Harrington said, "the first thing we'd want to demonstrate is that they can be introduced into primary, freshly isolated human cells. Next, to show that they could go into stem cells, which can be used in various ex vivo gene therapy applications."

The project leaders are also "very interested in developing animal models that would allow us to determine the safety and efficacy of our prototype HACs in a non-human system."

Harrington foresees their use "in gene therapy human clinical trials the ultimate goal we hope, in the next couple of years." The first such applications, he concluded, "are expected to be in treating disorders such as AIDS, sickle-cell anemia, beta-thalassemia, cystic fibrosis and muscular dystrophy."

An editorial accompanying the Case Western paper in Nature Genetics called it "an important landmark in terms of constructing HACs. This is the first time that a mitotically and cytogenetically stable artificial chromosome derived from transfected DNA has been generated." n

LANGUAGE: ENGLISH

LOAD-DATE: April 2, 1997

39TH STORY of Level 1 printed in FULL format.

BIOWORLD Today

April 15, 1997

SECTION: VOL. 8; No. 72

LENGTH: 1208 words

HEADLINE: CLOCK TICKS FOR NATIONAL BIOETHICS COMMISSION AS CLONING ISSUE IS SCRUTINIZED

BYLINE: Seachrist, Lisa

BODY:

By Lisa Seachrist Washington Editor WASHINGTON With its deadline for makings ome recommendations on cloning to President Clinton looming six weeks ahead, the National Bioethics Advisory Commission (NBAC) is leaning toward proposing a federal ban on research efforts that would result in producing a cloned human baby.The commission, however, appears hesitant to weigh in on research in human tissues that stops short of implanting a cloned embryo the types of research on human eggs and DNA that could result in new cell and tissue therapies for fear of simply renewing the human embryo research debate.

"We have a lot to do here," said NBAC chairman and Princeton University President Harold Shapiro. "But, for a wide variety of reasons, everyone seems to be saying they want a barrier to human cloning now. Here is an easier area to reach a conclusion."

NBAC entertained religious, legal, scientific and ethical points of view at its meeting in March. Shapiro divided the issues into three "buckets" to contain the various questions that will come to play in any policy recommendations and assigned the commissioners to participate in one of the discussion "buckets."

Bernard Lo, a medical ethicist at the University of California, San Francisco, lead the ethical discussion, which focused on which consideration was strong enough to continue the moratorium: whether those who wished to clone or those who wished to prevent cloning had the burden of proof, and what arguments would justify a permanent ban.

"We had a lot of support for continuing the moratorium," Lo said, "but we couldn't pinpoint any one objection that was telling. Instead, it was a cumulative effect that may justify a continuation of the moratorium. And we didn't begin to touch upon the research that would lead up to cloning a human."

The ethical "bucket," however, did try to assess whether there was an inherent right to reproduction and, if there was, whether these were limits to that right. They weighed that view against concerns discussed during the religious perspectives meeting in March, which include undue expectations of a cloned human, disruption of the family unit as well as problems in identifying one's genetic parents.

Nevertheless, the ethical discussion found some difficulty incorporating religious views because they weren't stated in secular language.

"Some people said that is demeans our belief to ask us to state it in secular terms," Lo said. "It is difficult because many of these objections do have weight, but many religious representatives feel it shows disrespect to ask for different language."

Thomas Murray, an ethicist at Case Western Reserve University, in Cleveland, who asked several of the speakers in the March meeting to state their objections in secular terms, pointed out that the commission "can't just give veto power to anyone with a strong belief. We don't do that with blood transfusions even though some find that procedure offensive."

Attempting To Regulate That Which Doesn't Exist

Even though these types of considerations will be important in developing policy actions for the committee, several members questioned whether it was necessary to address human cloning when cloning as yet doesn't exist. Stuart Orkin, professor of pediatric medicine at Harvard Medical School, and Janet Rossant, senior scientist at Mount Sinai Hospital, in Toronto, served as cloning experts and presented some of the scientific issues to the committee.

Rossant noted that species differences may prevent human cloning from ever happening. In addition, she pointed out that there are completely differentiated cells in most tissues and it is unclear that the donor cell used to create the cloned sheep "Dolly" was indeed a fully differentiated cell.

"It is possible that imprinting may result in developmental problems," Rossant said. "There is also some risk to the cloned human as a result of using old DNA it may result in a shortened life and they have begun to accumulate mutations that could cause problems."

Orkin presented the list of steps that good science would follow before attempting to create a human clone. Orkin maintains that science today is in phase one basic research into animal cloning and the cellular mechanisms controlling reprogramming of the DNA. Phase two, which is not yet happening, would include experimentation on early embryos not intended for implementation. Phase three would include generating differentiated cells as cellular therapies and phase four would be implanting an embryo produced by nuclear transfer in order to produce a human being.

"At this time period, implanting, in addition to ethical concerns, is just bad science," Orkin said. "We need more information from animal experiments."

Ezekial Emmanuel, professor of medicine at the Dana-Farber Cancer Institute, in Boston, asked whether, for the time being, animal research provides enough information. Rossant responded, "For now, there is a great deal of animal research that needs to be done. But I don't see how any cellular therapies are going to arise without moving to experiments with human eggs and producing a human embryo."

Because of a ban on human embryo research written into the appropriations legislation for the National Institutes of Health, there is no government funding for, and consequently no oversight of, human embryo research. For that

reason, the legal "bucket" explored all of the policy options for two different activities that Alta Charo, professor of law at the University of Wisconsin, Madison, described as "baby-making and everything else."

For "everything else," Charo described the policy options as total permission, including federal funding, permissibility without federal funding, conditional permissibility without federal funding and rules that restrict use in humans, until adequate information in animals is obtained, or a total prohibition.

"It is important to realize that federal funding may slow down the introduction of this technology into the clinic," Charo said.

In the "baby-making" scenario, Alexander Capron described the policy options as full federal funding, conditional permissibility without federal funding and protections in place for the gestating woman and consent to using DNA, or a total prohibition.

"We all agree about baby-making.'" Eric Cassell, professor of public health at Cornell Medical College, in New York, said. "But how do we get at the private sector?"

Charo noted that with the current ban on human embryo research, some doctors in the fertility field have patients pay for services that are basically unproven experimental therapies that take place outside of clinical protocols without any outside review.

Charo advocates the extension of basic human subject protections informed consent and outside protocol review to all citizens in the U.S. Currently, human subject protections apply for those participating in research funded by the National Institutes of Health, those participating in studies that will be reviewed by FDA and those participating in research sponsored by a few other government agencies.

NBAC plans to meet twice in May in order to prepare policy recommendations for the president.

LANGUAGE: ENGLISH

LOAD-DATE: April 16, 1997

June, 1990

SECTION: Vol. 265 ; No. 6 ; Pg. 40; ISSN: 0276-9077

LENGTH: 3736 words

HEADLINE: Getting the bugs out; agricultural use of genetically altered bacteria

BYLINE: Baskin, Yvonne

BODY:

IN THE SPRING of 1987 California scientists removed the lids from a few petri dishes, scraped out yellowish-white blotches that smelled like sweaty feet, diluted the material in water, and sprayed it on a tiny patch of potatoes and another of strawberries. With the spraying, genetically engineered microbes made their much delayed debut in the environment.

The blotches were colonies of bacteria, nicknamed "ice minus," that had been altered in a laboratory so that they would protect plants from mild frosts. Boosters of biotechnology predicted that ice minus would soon be joined by microbes genetically altered to kill caterpillars and weevils, supply nitrogen to the roots of plants, and eliminate the increasing and undisputed menace to the environment of chemical pesticides and fertilizers.

Alternatives to farm chemicals are hardly a new dream, In her landmark 1962 book Silent Spring, Rachel Carson urged the nation to take "the other road," to seek biological solutions, based on understanding of the living organisms they seek to control, and of the whole fabric of life to which these organisms belong." The dream, however, remains largely unfulfilled. Researchers have identified some 1,500 microorganisms or microbial toxins with the potential to control insects. But in their naturally occurring forms most have proved too short-lived, too slow to kill, and too narrowly specific in their effects to oust chemicals from the farm. Only nineteen microorganisms-eleven bacteria, four viruses, three fungi, and one protozoan-have been registered as pesticides by the Environmental Protection Agency, as compared with some 640 chemicals, used in 24,000 pesticide products. In some areas the introduction of wasps and other predators has successfully controlled insect pests. Altogether, however, only one percent of the world's 10,000 crop pests can now be controlled effectively by natural biological methods.

With the advent of genetic-engineering techniques, in the mid-1970s, biologists held out the hope that many of the drawbacks to pest control by microbes could be overcome. But in the early 1980s, when agricultural researchers began trying to enhance the efficiency of biological agents through genetic engineering, not everyone perceived it as the fulfillment of Carson's dream. Indeed, when the plant pathologist Steven Lindow first sought permission, in 1982, to field-test ice minus, he aroused the nation's misapprehensions, not only about genetic engineering but also about technology in general. It took five years of congressional scrutiny, public hearings, lawsuits, ever-shifting regulatory hurdles, and even vandalism of the fields before Lindow and

Advanced Genetic Sciences, a small Oakland, California, biotech firm that had license to use his concept, were allowed to spray their microbes outdoors.

To those of us who gathered for the events, near Brentwood, in California's Central Valley, and at Tulelake, California, on the Oregon border, the signs of the nation's anxiety were unmistakable. Both patches of land were surrounded by metal towers and stakes laden with EPA air-monitoring equipment. By regulatory fiat the researchers wore "moonsuits" and respirators as they sprayed, creating an ominous tableau for the television cameras.

These dramatic precautions were abandoned within months. Regardless, only half a dozen live, genetically engineered microorganisms have followed ice minus out of the lab. None is available to farmers. The technique remains, as one biotech executive put it, in an "intellectual cul-de-sac," trapped there by public perceptions and a formidable regulatory scheme.

Just what is this ice-minus bacterium? Where does it come from? How does it work? How do we know whether it poses any threat at all to the environment?

FARMERS IN THE northern half of the United States spend millions of dollars a year on frost protection: smudge pots to heat the air, sprinklers to wet the crop, wind machines and helicopters to mix the cold ground layer with warmer air aloft, and artificial fogs or foam blankets to prevent heat loss from the ground. Still, they lose as much as $ 3 billion a year in direct damage from mild frosts. Perhaps more important, the threat of frost limits both the growing season and the northern range of crops.

Traditional plant breeders, who engineer the genes of crop plants simply by selecting successful strains, have pushed back some of these limits. Since the turn of the century they have extended the northern range of corn on this continent by 200 miles and brought wheat to the northern Canadian prairies. Plant biologists are now trying to pinpoint the genes that confer frost-hardiness or rapid maturation, in order eventually to enhance them or to endow more-vulnerable crops with their powers.

Genetic engineering of hardier crops seems to farmers I have spoken with to be a natural extension of plant breeding. Designing bacteria to control frost, however, strikes them as bizarre and unnatural. Yet this concept, too, had its beginnings in a cornfield. It was the serendipitous spinoff, in an odd, backwards sort of way, of a traditional plant-breeding experiment.

The story begins with Paul Hoppe, a U.S. Department of Agriculture corn pathologist at the University of Wisconsin, who was laboring during the 1940s and 1950s to breed new strains of fungus-resistant corn. To ensure that his plants were challenged by fungal epidemics, he would grind up infected corn leaves from the previous Year's crop and sprinkle them on the field. He did this as usual in June of 1961. Two weeks later a late freeze hit the Midwest. The plants sprinkled with dried corn leaves were killed. The rest survived.

When Steven Lindow arrived at Wisconsin twelve years later to work on his doctorate, "this weird thing about corn plants," as he now describes it, was presented to him. Was there something about the infected leaves that enhanced a plant's sensitivity to cold? He pursued the matter first as a biochemistry problem, making active extracts from the old leaves and searching for a chemical that made young leaves vulnerable. Then one day he added a bactericide to the

extracts and the frost-enhancing activity stopped. He began isolating and testing dozens of strains of bacteria from his leaf extracts, trying to find which ones somehow increased a plant's susceptibility to low temperatures. In early 1975 his thirty-first isolate gave him an answer.

Lindow had a refrigerator loaded with test tubes full of water and colonies of bacteria that he had isolated from the corn leaves. When he went to the refrigerator one day, he found that the temperature had dipped a little below freezing. Every tube of bacterium No. 31 had frozen. None of the others had.

Water doesn't necessarily turn to ice at 32 degrees F Small amounts of pure distilled water can remain liquid at temperatures as low as -40 degrees C a phenomenon called supercooling. Even large amounts of pure water readily supercool to 14 degrees . Drop a catalyst-a nucleating agent that helps orient the water molecules into an ice-like lattice-into a flask of supercooled water and the water will instantly, dramatically, crystallize into ice. Or lower the temperature further and random groupings of water molecules will trigger this phase shift spontaneously.

Lindow soon established that bacterium No. 31, a strain of common leaf bacteria called Pseudomonas syringae, has a protein in its cell membrane that can nucleate ice. In fact, this so-called ice-plus microbe has turned out to be one of the most effective ice nucleators known.

Plants are 90 percent water, and water in plant tissues can supercool. Lindow began to wonder: do the ice-nucleating bacteria that live on plants' stems and leaves limit supercooling and allow damaging ice crystals to form inside the plants' tissues at warmer temperatures? In a greenhouse he grew plants under aseptic, or microbe-free, conditions, and found they could tolerate temperatures as low as 23 degrees . When he sprayed the plants with ice-nucleating P. syringae, they froze at 28 degrees . Lindow began washing bacteria from the leaves of dozens of plant species, both crops and weeds; he found ice-nucleating strains on leaf surfaces everywhere. Anywhere from a tenth of a percent to ten percent of the bacteria on a leaf surface may be capable of nucleating ice, he discovered. Of all the ice-plus strains, P. syringae turned out to be the most common. You probably eat it in every salad," he told me.

In growth chambers and field plots Lindow began testing various ways of manipulating the microbial populations on corn leaves: killing off all microbes with antibiotics, for example, or coating the leaves with detergents and heavy metals, such as zinc and copper, to inhibit ice nucleation. He also tried something else: spraying plants with bacteria that are naturally ice-minus-that is, bacteria that are essentially neutral and do not possess an ice-nucleating capability-to make sure that plant surfaces were too full to support later-arriving ice-nucleating cousins.

The results confirmed that frost damage declines as the ice-plus population shrinks. But detergents, heavy metals, and antibiotics either are toxic to plants or provide frost protection too short-lived to be widely practical on the farm. And the natural ice-minus bacteria competed poorly with the ice-nucleating ones. Not until he had completed his Ph.D., in 1978, and accepted a faculty post at the University of California-Berkeley, did Lindow begin to consider the possibility of genetic manipulation of P. syringae.

For every protein an organism makes, it must carry a gene that encodes the blueprint for it. Knock out the so-called ice gene and the bacterium would be unable to make the ice-nucleating protein. Lindow's team made its first ice-minus mutants not by genetic engineering but by the more traditional (and still largely unregulated) technique of exposing bacteria to mutagenic chemicals. A decade ago, with no fanfare or need for federal approval, they sprayed these mutant bugs on potatoes in a field near Tulelake.

But chemicals-and radiation, which is also sometimes used-are crude. They mutate multiple genes, not just the targeted trait, and leave the bugs "sick in subtle ways," Lindow explained to me. So in 1981, when genetic-engineering techniques became available for manipulating P. syringae, his team set out to locate the ice gene and remove it precisely, without causing other, haphazard damage. They started with no idea where among the bacteria's 3,000 genes the ice gene might be, or what its protein product looked like. In the lab one day Douglas Gurian-Sherman, a graduate student, walked me through the process they used.

"THINK OF THE bacteria as plastic bags filled with DNA and other stuff," he said. "You want to break them open and then separate the DNA from the other components." The terminology-breaking, loading, cutting, splicing, inserting-suggests a dramatically mechanical, almost surgical operation. In truth, I found, genetic engineering is a chemical and enzymatic process, to the naked eye a seemingly endless mixing and separating of clear liquids. First enzymes, detergents, and acidic compounds are added to a bacterial suspension to lyase, or cat away, the outer membranes of the bacteria. The resulting liquid is spun in a centrifuge to separate out the DNA, which differs in weight and density from other organic molecules inside the bacterial cell.

Once the DNA of P. syringae was isolated, the next step was to chop it into fragments, one of which would carry the ice gene. The chopping was done with restriction enzymes, popularly referred to as "chemical scissors." Like most of the tools of genetic engineering, these enzymes had originally been isolated from microbes, which use them to disable invading viruses or to cut and splice their own DNA for replication and repair. Researchers now buy dozens of kinds of these enzymes off the shelf.

It is the specificity of the various restriction enzymes that gives genetic engineering its precision. DNA is formed in a linear sequence composed of four chemical bases-adenine, thymine, guanine, cytosine (ATGC)-strung along two complementary strands. A is always found paired with T, G with C. The sequence of bases GAATTC on one strand, for example, will always be paired with CTTAAG on the other, the pairs linked like the teeth of a zipper, the whole zipper-like sequence twisted into a double helical shape. When a restriction enzyme called EcoR1 recognizes the six-base-pair pattern GAATTC and its complement, it will make a staggered cut in the double strands, slicing each strand between the A and the G. This leaves an AATT tail on one cut end and a TTAA tail on the other-so-called "sticky ends," single-stranded and eager to link up with a complementary match.

"Often the whole thing is done in a test tube about this big," Gurian-Sherman said. He was holding up a one-inch vial. "You might have a solution of DNA that's half the tube, and then you might add a tiny bit of this enzyme. A tiny bit of another. And usually a buffer solution." Once the DNA is chopped, the researchers generate thousands of copies of each fragment by

inserting each into a bacterium for cloning. The first step toward cloning is splicing each fragment onto a small segment of viral DNA called a cosmid. "From a supplier you buy what are called right and left arms," Gurian-Sherman said. "You just take your fragments and your cosmid arms and mix them. Both need to have been cut with the same restriction enzymes, so that they have sticky ends, ready to link up."

To begin to create an ice-minus version of P syringae, Lindow's team took these cosmid-linked fragments of P. syringae DNA and presented them to tiny viruses, called phages, that attack bacteria and use the bacteria's cellular machinery to produce multiple new viruses. "The phage sees the cosmid DNA, recognizes it, and pulls it in just as if it were winding string onto a spool," Gurian-Sherman said. The phages were then allowed to infect Escherichia coli, a bacterium that has become the white mouse of genetic engineering. Inside E. coli the viral DNA multiplied freely, making thousands of clones of the P. syringae fragments with the cosmid DNA.

Which bacterial colonies carried the fragments with the ice gene? E. coli are naturally ice-minus, and so Lindow's team picked out the ones that now nucleated ice. Then, to isolate the gene further, the researchers did what is called subcloning. Essentially, they removed the fragment and started over, repeating the whole process several times, using ever smaller lengths of DNA. In mid-1982 the team announced the isolation of the ice gene itself-the smallest fragment of P. syringae DNA that could turn an ice-minus bug ice-plus.

Once they had the gene, the researchers gutted it by cutting a chunk out of the center with restriction enzymes and rejoining the ends. Their next move was to insert this crippled gene into the parent strains of P. syringae that still carried full copies of the ice gene. This was done by encouraging mating and "conjugal transmission" of the crippled gene from the E. coli to P. syringae. Putting the two strains of bacteria together on a petri dish for several hours is encouragement enough for mating to occur.

By manipulating the environment in the petri dish, Lindow also made it impossible for these P syringae to survive unless they not only accepted the crippled ice gene but also inserted it into their own chromosomes next to their good ice gene. For the few that survived this test, a final manipulation awaited. Lindow shifted the environment of the dish again, relieving the pressure on the bacteria to keep the new gene. He hoped that in a few of them the new gene would detach itself from the chromosome a little sloppily, taking along a chunk of the bug's own ice gene.

A few colonies of ice-minus P syringae, identical to their parents except for a single gene, were all that remained: yellowish-white blotches that smelled like sweaty feet and were no longer able to nucleate ice.

SINCE ITS inception, amid a barrage of frightening headlines in the mid-1970s, genetic-engineering research had been subject to guidelines laid down by the National Institutes of Health. Strict containment of all lab-altered creatures was the goal. No crises occurred, and gradually both public anxiety and federal oversight relaxed. Then, in 1982, Lindow proposed to field-test ice minus.

Congress called hearings. The Washington activist Jeremy Rifkin, an opponent of virtually every application of genetic engineering, filed the first in a

series of procedural lawsuits. Ecologists emphasized the problems created by non-native species such as gypsy moths and kudzu vines. In 1983 the EPA entered the fray by declaring ice minus a pesticide under the jurisdiction of the Federal Insecticide, Fungicide and Rodenticide Act. The rationale went like this: ice-plus bacteria encourage plants to freeze and thus are pests; ice minus, if it arrives first, blocks this pestiferous activity and thus is a pesticide. At the same time, the EPA ended its practice of exempting from scrutiny small-scale (under ten acres) field trials of microbial agents. To get permission to spray ice minus on a quarter-acre potato patch, Lindow faced an enormous array of lab tests and paperwork previously required only for products at well-advanced stages of commercialization.

By the time his experiment was approved, Lindow had filed more than 1,300 pages of applications and data with federal and state agencies. In labs and greenhouses he had tested ice minus for pathogenicity on seventy-five plants, from zinnias to sugar beets. He had run an extensive battery of "product identity" tests and scrutinized the bug's life-style preferences, all to make sure that it had no novel powers that might cause it to run amok.

Two seasons in the field-1987 and 1988-confirmed the bacterium's staid behavior, and also its ability to protect crops: potato seedlings coated with ice minus received only a third as much frost damage as unprotected plants. Lindow chose not to conduct a third field test last summer. Faced with regulatory uncertainty, ice minus's future on the farm is far from assured.

A few other lab-altered creatures did go to the fields last summer. BioTechnica Agriculture, of Overland Park, Kansas, tested several genetically modified strains of rhizobia, nitrogen-fixing bacteria that have long been used to foster the growth of alfalfa, soybeans, and other legumes. Crop Genetics International, of Hanover, Maryland, tested bacteria designed to protect against rice stem borers and European corn borers. These bacteria, which live inside the vascular systems of plants, had been outfitted with toxin genes taken from another bug, Bacillus thuringiensis, or BT, a natural microbial pesticide sold in the United States since 1961.

None of the tested bugs have ventured away from their release sites or persisted in the environment. Undoubtedly they have changed for a time the mix of microbial populations in the soil or on leaves, but so do chemical pesticides and herbicides, and farm practices such as tilling, irrigation, and crop rotation. In May of 1988 a Congressional Office of Technology Assessment report concluded, "With adequate review none of the small-scale field tests proposed or probable within the next several years are likely to result in an environmental problem that would be widespread or difficult to control."

HERE is still no consensus, however, on what constitutes "adequate review." A draft proposal for revising the EPA regulations was circulated in the last months of the Reagan Administration, but it drew criticism from all sides and finally died at the Office of Management and Budget. A key provision would have created a number of local environmental-biosafety committees to assume some unspecified oversight role. The EPA also proposed to broaden the scope of the Toxic Substances Control Act to oversee work with naturally occurring organisms. Industry argued that the EPA should move in the opposite direction, exempting all or most small-scale research with microbes. Environmentalists oppose such an exemption but also don't want the EPA squandering its regulatory energies on bugs commonly found in compost heaps or sewage ponds.

The EPA and the White House are currently working out the Bush Administration's position. No one, however, expects any dramatic shifts in the regulations. With major environmental legislation like the Clean Air Act under review, genetically engineered microbes have not been a priority on anyone's agenda this year.

Many in the biotech industry echo the sentiments of Jerry Caulder, the president of Mycogen Corporation, who believes that the current regulations would work well "if we didn't have people coming along playing what-if to the nth degree on every release." He adds, "The EPA is in a terrible position. The regulations are supposed to be scientifically reasonable, and yet the public wants an assurance of absolute safety. You really can't do both." The EPA has no equivalent of the medical-research community's clinical trial, in which new therapies are evaluated in relation to standard ones, allowing the better of two often imperfect alternatives to be determined.

The 1988 OTA report stated,

> In evaluating the potential risks associated with these new technologies, the appropriate question is not "How can we reduce the potential risks to zero?" but "What are the relative risks of the new technologies compared with the risks of the technologies with which they will compete?" Furthermore, What are the risks posed by over-regulating, or failing to develop fully the new technologies? How do we weigh costs and benefits? How much review is enough?

Until such questions have been answered satisfactorily and the answers guide our regulatory strategies, we will have little choice but to keep relying on the chemical pesticides and fertilizers whose harmful effects are already apparent.

- Yvonne Baskin

GRAPHIC: Photograph

7TH STORY of Level 1 printed in FULL format.

R & D Focus Drug News

May 5, 1997

LENGTH: 176 words

HEADLINE: gene discovery, metabolic disease, deCODE genetics deCODE genetics licensing offer, Worldwide

BYLINE: Smarason, Hannes T

BODY:

A gene discovery program is under way with deCODE genetics (Iceland) to find genes associated with metabolic diseases such as diabetes, utilizing access to Iceland's uniquely homogeneous population. The company is constructing an anonymous database (GGPR) comprised of genotypes, genealogy, phenotypes and resource information in conjunction with the Icelandic government, and will use the database along with a proprietary bioinformatics platform to rapidly identify the genetic basis of diseases. Potential disease-causing genes will be cloned using positional cloning techniques. deCODE genetics hopes to establish corporate collaborations for gene discovery and characterization, product development, and nonexclusive licensing rights to the GGPR database. Data on the company's research activities were presented at the 5th European Life Sciences Conference, 20-22 April 1997, Amsterdam (Netherlands).gene discovery, metabolic disease, deCODE genetics, A10X, Other Drugs Used In Diabetes, deCODE genetics, licensing-offer, Worldwide, new-drug.

LANGUAGE: ENGLISH

LOAD-DATE: May 5, 1997

New Scientist

April 26, 1997

SECTION: Forum, Pg. 47

LENGTH: 4827 words

HEADLINE: Promises, promises

HIGHLIGHT: From extra cash to better access to the Net, all three parties claim to be on the side of science. Here's how they measure up in New Scientist 's 1997 election call

BODY:

Sweden dedicates 3.3 per cent of its GDP to research and development, Japan 2.9 per cent and the US 2.5 per cent. France and Germany spend 2.4 and 2.3 per cent respectively. At 2.2 per cent, Britain spends below them all. What percentage of the nation's GDP do you think should go to science ? If you think Britain has it right, does that mean the others are just being inefficient ?

Conservatives: The key indicator is not R&D expenditure, but its impact, and it is clear that British science punches well above its weight. With only 1 per cent of the world's population we generate 6 per cent of its research, 8 per cent of science publications and 9 per cent of citations. We are the most cost-effective producer of research among the G7 countries, many of which are now restraining their science budgets.

Labour: The percentage of GDP spent on science and technology is only one of several indicators of the underlying strength of a nation's science base. Once in government, Labour will develop criteria to assess the quality as well as the quantity of investment.

Liberal Democrats: Britain spends far too little on its science base. The current percentage of GDP spent on science is far too low. Liberal Democrats would immediately increase it by shifting funds from the military R&D budget to civilian research. For far too long other countries have been ahead of us in their investment; our scientists must be enabled to compete on a level footing.

Do you believe that labs set up to give impartial advice, such as the Institute of Animal Health and the Laboratory of the Government Chemist, should operate in the private sector ? If they do operate in the private sector, what steps should be taken to ensure their impartiality ?

Conservatives: Whether in the public or private sectors, laboratories have a professional duty to be impartial. The prior options review process has rigorously evaluated the individual status of each of the public sector research establishments (PSREs). In some cases, it was clear that they should continue to be in the public sector, in others that they should enjoy agency status and in yet others that they can best flourish in the private sector. Such decisions are made after full consultation, to secure the best future for each establishment.

Labour: The government's prior options review of government labs was driven more by Conservative privatisation ideology than by what is best for our

nation's science base. The PSREs are a major national resource and a source of crucial research expertise, and they have a vital role to play in offering independent, impartial advice to government and the private sector. We welcome the fact that the government's prior options review concluded that most PSREs should remain in the public sector.

We will work with the new management in establishments such as the Laboratory of the Government Chemist, which have already been transferred into the private sector, and ensure that the channels to offer impartial advice to ministers remain open.

Liberal Democrats: It is only in the public sector that we can be sure of absolute impartiality. A laboratory set up to investigate food safety but funded by a supermarket chain might be serving an agenda not in the public interest.

The end of the prior options review, designed to privatise government laboratories, was good news. Constant reviews damage morale and often waste time.

Should government research funding be more concentrated within a "superleague" of universities ?

Conservatives: It is only fair, as well as efficient, that university departments which achieve excellence in their research should be rewarded with further funds. That encourages success and international excellence. But all departments are able to enter into research contracts, including with the private sector, and many are doing so successfully.

Labour: Labour will await the conclusions of the Dearing inquiry into the future of higher education before deciding policy in this area.

Liberal Democrats: The issue of selectivity and direction of resources in science is highly contentious. Some element of selectivity is inevitable: there is never going to be enough to satisfy all demands. Rationing therefore has to take place and priorities have to be set.

The increasing expense of research means that it makes sense to concentrate a fair amount of funding on a limited number of well-equipped centres. However, there has been large-scale government neglect of funding for equipment.

Liberal Democrats would make annual grants to eliminate the backlog of obsolete buildings and equipment as part of our proposed increase in the science budget. Under Liberal Democrat policy all universities would get more funding.

According to the last "R&D Scoreboard", an international league table of corporate research spending, companies worldwide spent on average 4.4 per cent of their total sales revenue on research. British firms on average devoted only 2.5 per cent. What should government do to encourage British firms to spend more on research ?

Conservatives: It was the Conservatives who initiated the R&D Scoreboard to show up the relative efforts of British companies. The government has encouraged British firms to spend more on research by working to improve the links between business and the science base. The Foresight programme is a prime example of how businesses and academics can come together to mutual advantage. The Teaching

Companies Scheme also reinforces links. In addition, specific programmes such as SMART, SPUR and the Crusade for Biotechnology provide direct incentives for companies to increase their investment in R&D.

Labour: It is a matter of concern that there is only one British company in the R&D Scoreboard top 50. Labour has already set up a corporate tax review to examine obstacles to all types of private sector investment, including R&D. We want to encourage a longer-term view of investment by industry. We will encourage the Design Council's work in promoting best practice in the private sector. This will increase the awareness within management of the importance of a carefully structured programme of research, design and development. Companies should publish details of their R&D expenditure to focus the minds of managers and aid comparison between firms.

Liberal Democrats: We would set up regionally based development agencies to bring together the functions of Department of Trade and Industry regional offices. The agencies would operate as regional organisations responsible to local authorities and, eventually, as part of our programme for regional government.

Liberal Democrats would develop a new pool of seed-corn funding to be administered by the regional development agencies and used either on its own or as leverage for other public (EU, City Challenge, and so on) or private-sector (banks, business angels) funding. Links with universities would also encourage companies to invest in research because they could see what was available and invest in research projects which interested them.

How will you measure the impact of Foresight ?

Conservatives: The impact of Foresight will be measured by the extent to which it influences corporate policy and investment decisions. There is already evidence that Foresight is embedding new thinking into companies' decision-making.

Labour: Labour will undertake a comprehensive audit of the Foresight programme to re-examine the way in which government should be involved in the funding of basic research activity. Labour will put in place effective mechanisms to ensure that there is a coordinated approach across all government departments in the dissemination and understanding of the Foresight findings. The remit of the work done by the Foresight panels will be broadened to encompass quality of life issues as well as wealth creation. Environmental, ecological and ethical issues would be taken more into account than has been the case to date.

Technology Foresight will be judged on the way in which it generates a significantly increased level of R&D spending within the economy; by the creation of new spin-off companies in the high-tech, high value-added sector of the economy; through the effectiveness of technology-transfer activity between the public and private sectors and within the private sector; and, in the closer and more deeply embedded relationship between our university research base and industry.

Liberal Democrats: The impact of Foresight can be measured by the number of research projects started through it and the number of companies more able to compete as a result of it. If companies start to invest in research through

Foresight and continue to do so then it will have succeeded.

Will you create a food safety authority, separate from agricultural interests and with statutory powers, along the lines of the American Food and Drug Administration ?

Conservatives: The Prime Minister has indicated that he will consider the possibility of introducing an independent food safety authority, but is inclined to believe that the current system of direct ministerial accountability provides greater safeguards for the public than this alternative.

Labour: Yes. Labour's agriculture, fisheries and food team, headed by Gavin Strang, has made a clear commitment to setting up an independent food standards agency, which will see itself as the consumer's champion. Its overriding priority will be the safety and quality of our food, all the way through the production and transportation process, from plough to plate. Food labelling will also come within its remit. It will monitor the enforcement of food safety regulations and will provide advice to the government on long-term food policy issues and research.

We will transfer resources from existing government departments, including the Ministry of Agriculture Fisheries and Food (MAFF), to the independent agency. Its advice and recommendations will be made public. It would report to Parliament and to the secretaries of state for health and for food and agriculture. It will act as one point of contact for government, consumers and industry - as opposed to the 43 different quangos across various departments that currently cover these issues.

Tony Blair has already asked Philip James, director of the Rowett Research Institute in Aberdeen and a renowned authority on food standards and nutrition, to begin work on the agency's remit.

Liberal Democrats: It has long been Liberal Democrat policy to create an independent food commission accountable to Parliament to separate the representation of producer and consumer. It is ridiculous that MAFF represents both producer and consumer, farmer and general public. The different functions of MAFF and the Department of Health should be separate to prevent a conflict of interest.

In the US, many scientific advisory meetings are conducted in public. In Britain, very few are. Would you make more such meetings, for example, those of the new Human Genetics Advisory Commission, open to the public ?

Conservatives: This is a matter for the committees themselves. We have agreed that their reports should be published, but it has to be for them to determine which parts, if any, of their deliberations need to be held in confidence.

Labour: Labour is committed to improving the public understanding of science and greater awareness of the importance of scientific progress to our quality of life. One of the ways to do this is to encourage a greater level of informed debate about the ethical implications of scientific advance. We are currently investigating ways in which to improve the level of informed debate on science in Britain.

Consensus conferences, where selected members of the public are brought together to deliberate then come to a consensus on a difficult issue, such as the ethics of cloning, are used to good effect elsewhere in Europe, and have now been introduced here through an initiative of the Biotechnology and Biological Sciences Research Council.

Liberal Democrats: Liberal Democrats would introduce a Freedom of Information Bill and encourage openness in all areas. By holding meetings in public, we will make sure that advisory committees are accountable to the public. We will also publish all results so that everyone is aware of important findings.

Would you support an international tax on aviation fuel as part of a programme to curb global warming ? Do you believe that taxation has a role in meeting any future environmental targets, domestic or international ?

Conservatives: We do not support an international tax on aviation fuel, as fiscal matters must be the responsibility of national governments. Domestically, however, we have given taxation a central role in promoting environmental objectives. We increased the level of fuel duty specifically to promote more environmentally conscious transport choices, and introduced the landfill tax, which goes directly to reduce employers' national insurance contributions.

Labour: Labour's environmental policy document In Trust for Tomorrow states that we are committed to a long-term, gradual change in the way the economy is organised, to ensure that it encourages "goods" such as employment, value-added production, investment and savings and discourages "bads" such as pollution and resource depletion. There are various different policy tools that can be used to achieve this, but each needs to be considered carefully.

Liberal Democrats: Liberal Democrats believe that taxation has a role to play in cutting down pollution. We would cut Vehicle Excise Duty on smaller, more fuel-efficient cars to only pounds 10, from the current pounds 145, by raising fuel duty by about 3p. This would encourage people to drive less polluting cars. Combined with investment in public transport, pursuing this policy would cut down on pollution significantly.

All parties have talked of money for computer equipment for schoolchildren. But the real costs will be in training teachers, maintaining the equipment and upgrading it regularly. Which department will this money come from and how much will you pledge ?

Conservatives: Departments across government share a responsibility for investing in computers. Only the US has a comparable ratio of personal computers to pupils. This year, pounds 132 million has been made available for information technology in schools within the Grant for Education Support and Training scheme. In addition, we have announced that after the millennium, all the proceeds of the National Lottery currently given to the Millennium Fund will go to a new pounds 300-million Information and Communication Technology Fund to invest in IT, including in schools.

Labour: There are four pillars of Labour's pledge to deliver to every pupil the educational benefits of the new information technologies. First, we agreed with British Telecom in September 1995 that as part of the phased

liberalisation of the home entertainments market they would connect every school, college, university and library to the information superhighway. The cable companies have indicated that they will also do this.

Second, we are in discussions with BT and other telecoms providers to ensure that their commitment to keep the costs of access to the Internet as low as possible.

Third, Tony Blair announced in October 1996 that we will establish a National Grid for Learning by providing high-quality content and access to software to make the superhighway work for schools, colleges and universities in the near future.

We envisage that this would be run as a public-private partnership, with government licensing the provider. The right to establish and run the service will be awarded to the consortium best able to bring together relevant software and educational experience along with financial backing.

The service will be free to schools, and self-financing, raising revenues from charging software companies and possibly from advertising and sponsorship.

The fourth pillar concerns hardware and teacher training. David Blunkett has pledged that Labour's University for Industry will include a Teachers' Centre for professional development.

Liberal Democrats: Liberal Democrats are committed to investment in education. Our policy of putting an extra penny on the basic rate of income tax is long-established. Some of the money raised would be spent on computer equipment for schools. Primary schools with over 250 pupils would receive pounds 16 000 for books, computers and equipment.

Teachers would be trained in information technology while they were at teacher training college and would be able to go back for refresher courses to make sure that they were up to speed on the latest technology. Local authorities would employ computer consultants to maintain and upgrade the equipment and buying in bulk would keep the price down.

Many small biotechnology and high-tech firms starve in their infancy for lack of funds. Would your government consider sponsored loans schemes to give them a fighting chance ?

Conservatives: The government's Biotechnology Means Business programme has been established specifically to encourage firms to exploit the potential of biotechnology. The SMART and SPUR schemes provide substantial assistance to small firms making use of new technology. In addition, the government's Small Firms Loan Guarantee Scheme provides biotech and high-tech firms with underwritten loans.

Earlier this year, we announced that we will encourage more investors with experience of high-tech businesses to lend their expertise to the scheme to boost further the take-up by such firms.

Labour: The Labour Party is supportive of the European draft directive on gene patenting which, if adopted, will help provide the stable regulatory environment within which essential biotechnology investment can take place

throughout the European Union.

Labour also supports the Biotechnology Means Business initiative belatedly launched by this government, although we fear that it is more concerned with window-dressing than providing effective support. The biotech sector is an area where Britain has a distinct lead over other European countries and ranks second only to the US. Labour's corporate tax review will be examining obstacles to investment in this sector as in many other areas of cutting-edge technology.

Liberal Democrats: The regional development centres, as mentioned earlier, would use a new pool of funding to help developing companies with the cost of employing scientists and engineers.

We would also encourage banks to establish regional investment funds to help small businesses at the local level, for instance, by lending on the basis of individuals and their records, rather than on the value of their property.

For more science news see http://www.newscientist.com

LANGUAGE: English

TYPE: Forum

LOAD-DATE: April 25, 1997

12TH STORY of Level 1 printed in FULL format.

U.S. News & World Report

March 17, 1997

SECTION: U.S. NEWS; U.S. NEWS IN BRIEF; Pg. 36

LENGTH: 751 words

HEADLINE: Keeping snoops out of health files; Cloning a flap over research; A disputed story threatens a trial; Who's to judge?

BYLINE: By Dana Hawkins; Traci Watson; Ted Gest; Gordon Witkin

HIGHLIGHT:
Privacy; Science; Terrorism; Courts

BODY:

PRIVACY

Keeping snoops out of health files

When a new mother comes home from the hospital these days, the bundle of mail awaiting her about cribs and diapers may outweigh her bundle of joy. How did the infant industry find out so fast?

Easy. Electronic medical records are now standard, and insurers, employers, researchers, and even marketing firms and creditors are collecting them for profit. Among the targets are detailed accounts of patient treatment and expenses, sought by HMOs in an effort to stem health costs. Many insurers formerly asked only for basic information on diagnoses.

Citing the increasing vulnerability of medical records, a National Research Council panel called last week for special software, encrypted passwords, and other measures to deny unauthorized outsiders access to sensitive files. Democratic Sen. Patrick Leahy of Vermont will propose limiting access to medical data and allowing patients to see and correct their records.

SCIENCE

Cloning a flap over research

It didn't take long for the cloning controversy to spread from biology to politics. Ethical alarms about the cloning of a sheep from one adult cell and of monkeys from embryo cells prompted President Clinton last week to ban federal funding for human-cloning research and some lawmakers to propose forbidding the process. With 87 percent of Americans saying they're against human cloning, politicians saw a rare chance to take a seemingly bold stand without alienating anyone.

The debate may lead to a repeat of the 1994 fuss over human embryo research. Clinton cut off federal funding, and Congress soon followed suit. As a result, there's no federal oversight of several studies that began without help from

Washington. "The great falsehood here is that research will go away," says David Adamson of the Society for Assisted Reproductive Technology. "It won't."

Funding squeeze. Even noncontroversial research has experienced a decline in federal support. A coalition of more than 20 scientific societies protested last week that the United States is shortchanging its research labs. When inflation is factored in, only two of the 10 federal agencies with large research portfolios have more science dollars this year than they did in 1994. Scientists want each agency's research budget to grow 7 percent next year. Yet White House aides and legislators note that science has won modest increases in austere times. "The government has an important role in science," says Tim Newell, a senior White House science adviser. "It's also important to balance the budget." Despite concerns that science is being stifled, it is likely that fiscal concerns will prevail.

COURTS

Who's to judge?

President Clinton is battling Senate Republicans over how best to fill nearly 100 vacancies in the 837-seat federal judiciary. Conservatives say he picks too many judicial activists; liberals want more gender and ethnic diversity. Clinton has named more women and minorities than his predecessors. Presidents Reagan and Bush averaged 11.8 percent women and 3.2 percent African-Americans.

TERRORISM

A disputed story threatens a trial

Can Oklahoma City bombing suspect Timothy McVeigh get a fair trial? That question hung in the crisp Colorado air last week amid fallout from a Dallas Morning News story claiming he had confessed.

The inflammatory impact on potential jurors could hardly be overstated; the article said McVeigh bombed the Murrah Federal Building during the day to ensure a "body count" that would grab the federal government's attention. (The April 1995 blast killed 168 and injured more than 500 others.) The story appeared soon after letters had been sent to about 700 prospective jurors from 23 counties in northeastern Colorado.

The trial, which could last two to four months, starts March 31. Meanwhile, McVeigh attorney Stephen Jones argues that the "confession" actually was a defense investigator's ruse to lure a potential witness into talking. The News stands by its story.

Judges appointed by Clinton

By gender		
Males	139	68.8 percent
Females	63	31.2 percent
By race		
Whites	146	72.3 percent
Blacks	38	18.8 percent

3RD STORY of Level 1 printed in FULL format.

Biotechnology Newswatch

March 3, 1997

SECTION: Pg. 1

LENGTH: 1131 words

HEADLINE: Cloning clamor aside, long leap seen from lamb to lad

BYLINE: MS, MP, MB

BODY:

Well, Hello Dolly.

While the little lamb's story is inspiring a flood of fantastic visions, from doomsday scenarios of thousands of Hitler clones to whimsical ways to create your better self, life on planet earth is a little more humdrum.

Despite all the hoopla about the possibility of cloning humans now that Dolly is among us, some scientists think the obstacles may well be insurmountable. Of course, nobody knows until the experiments are done, but there may be some technical reasons for profound skepticism regarding human cloning.

Colin Stewart, a biologist with the National Cancer Institute, suspects that sheep embryos may possess some characteristics that are unique in the animal kingdom.

In an editorial accompanying the report from Scotland's Roslin Institute on the lamb clone in the journal Nature, Stewart writes that the genetic material in sheep embryos start to replicate at the 8-16 cell stage, far later than the DNA in the embryos of other mammals, including humans.

The time lag may permit the DNA from an adult sheep to remodel itself into an embryonic state, forming a clone, but the process is unlikely to occur in other animals, he said in a telephone interview.

''It may not be possible to produce the same kind of results in other animals,'' said Stewart. DNA transcription begins at the 2-cell stage in mice and about the 4-cell stage in humans.

Of course, scientists had long dismissed the notion that it was possible to clone an animal from an adult cell.

But as one biologists quipped: ''Who would want to make a clone of themselves anyway? This is an applied technology that will have some industrial applications, but as far as basic research is concerned, I don't think it will be very useful.''

Other scientists battling in the trenches of research had a different take on the prospect of cloned animals.

''That kind of stuff is going to be great for us because we can have a uniform tissue to work on and we can study them in much better detail,'' said Nick Rampino, a cancer researcher at The Burnham Institute, of La Jolla, Calif.

Rampino, who is attempting to find out how tumor regulating genes work said that, ''a lot of the problem we have is that genetically we don't work with the same thing all the time. Even with genetically similar mice, you breed them and get genetic drift. It kind of puts a sense in this.''

The stunning display of technological prowess generated a whirlwind of press coverage about Dolly, Ian Wilmut, the 53-year-old embryologist who cloned her from a cell from another sheep's udder and PPL Therapeutics, the tiny, low-profile biotechnology company that owns the rights to the technique.

But financial analysts did not see the news sparking an immediate stampede of investors to the sector as a whole.

''This is very important scientific work; it maybe lends itself a little bit more to public imagination than other kinds of discoveries,'' said Meg Malloy, a biotech analyst with Hambrecht & Quist. ''But people should invest in the sector because of positive fundamentals.''

Malloy, who follows Genzyme, one of the companies developing transgenic animals that produce human proteins in milk, said that there would be no advantage to using the cloning technique at this time. Transgenic technology as a whole is still in the proof-of-principle stage, she said, and several steps removed from cloning.

Other companies working in this area include Novartis AG, Nextran and Alexion, which are developing transgenic animals that can be used as organ donors.

''Most of the public companies today are working so far afield from cloning technologies, I just don't see it really impacting. A lot of other issues go into biotech investing,'' she said.

Another analyst, Edward Hurwitz of Robertson, Stephens & Co., said that the achievement, and ''the fact that it happened as quickly as it did, when people thought it couldn't be done, is largely consistent with the way most of the field and this science has played out, which is the that discoveries have happened at an accelerated pace beyond anybody's expectations.''

He thinks progress in biotechnology will ''continue to surprise people,'' but the investors view cloning as a long-term issue.

''What drives these stock prices has to do more with clinical data, and revenue protections in the near-term, and this is too far out,'' he said.

The public and politicians reacted, for the most part, with fear about the chance the technology will be used to create human clones.

Sen. Christopher Bond (R-Mo.) called on the federal government to ''send a clear signal'' that cloning ''is something we cannot and should not tolerate.''

At the same time President Bill Clinton asked the National Bioethics Commission to examine the issue and report to him within 90 days on the legal and ethical ramifications of cloning, especially on what it means for humans. The president and congress will also be interested in recommendations on what, if anything should be done with legislation to control cloning.

In 1995 Clinton signed an executive order banning government funding for the creation of human embryos. At that time the target was in vitro fertilization, now it may be extended to human cloning.

Clinton spokesman Mike McCurry called cloning a very troubling subject and said White House polls showed 87 percent of Americans believed cloning of humans should be banned outright.

Carl Feldbaum, president of the Biotechnology Industry Organization, said that he ''can think of no ethical reason to apply this technique to human beings, if in fact it can be applied.''

Feldbaum believes that strict attention must be paid to the ethical implications of the discovery.

''The biotechnology industry exists to use genetic information to cure disease and improve agriculture. We opposed human cloning when it was a theory. Now that it may be possible, we urge that it be prohibited by law,'' he said in a statement.

France's farm minister Philippe Vasseur conjured up horror movie critters.

''Even if countries like France, Italy, Spain Germany and others have rigorous rules . . . about using science, what you can and cannot do, tomorrow someone could well invent sheep with eight feet or chickens with six legs,'' Vasseur said.

Long-time biotech foe Jeremy Rifkin sent out a terse press release, stating that the ''prospect of potential cloning of human beings marks one of the most significant scientific events of all time, challenging our most basic concept of reproduction on earth.''

He said his organization, The Foundation on Economic Trends, is ''determined to mount a global effort in opposition to human cloning, and will seek legislation to outlaw this technology in every nation.''

LANGUAGE: ENGLISH

LOAD-DATE: March 25, 1997

8TH STORY of Level 1 printed in FULL format.

November 13, 1992

SECTION: Vol. 258 ; No. 5085 ; Pg. 1216; ISSN: 0036-8075

LENGTH: 1813 words

HEADLINE: Black colleges cultivate scientists; includes related articles on enrollment boom and on 3 success stories; Special Section: Minorities in Science

BYLINE: Culotta, Elizabeth

BODY:

In the spring of 1981, North Carolina native B. Lee Stackhouse left all-black Hampton University in Hampton, Virginia, with at least two newly acquired assets: an M.S. in biology and the confidence that he could do a Ph.D. at a major university. Stackhouse, whose B.S. in biology is also from Hampton, decided to spend the summer as a research assistant in a cardiovascular research lab at Boston University, his initial foray into a mostly white environment. But his first taste of the world of big-time research was sour--so sour that he has never returned full-time to a majority institution.

He says that in the Boston lab, faculty members--and even his fellow students--treated him like a child, offering to write down the simplest instructions. In the city itself, security guards perked up when he entered grocery stores and followed him through the aisles. "If I'd gone to a majority undergrad institution I might have been accustomed to it," Stackhouse says. "But this hit me like a ton of bricks. I thought: 'Is this the way the country really is?'"

Stackhouse lasted out the summer, but in the fall, he headed back to Hampton, where he taught as an instructor for 2 years. Then he decided to get that Ph.D. after all--at historically black Howard University.

Like Stackhouse, an increasing number of black students are choosing black colleges. Overall enrollments have surged, especially at the undergraduate level, and the top black schools are flooded with applications. But how well do these schools teach science? Few can afford state-of-the-art instrumentation, and even fewer have a research tradition, scientists both inside and outside these schools agree. And the historically black colleges and universities (referred to as HBCUs) vary greatly in quality, with some small schools little better than junior colleges. Yet on the plus side, HBCUs provide a welcoming environment, personal attention from professors, and a plethora of role models who expect students to excel.

Howard grad Roosevelt Johnson, program director for graduate and postdoc programs at NSF, sums up the education at the best black colleges this way: "You come out with a very strong academic experience, but possibly a limited research experience."

Black pride. For many scientifically inclined students, the HBCU advantages apparently pay off. Although most blacks enter majority schools, black schools graduate more than their share of black scientists. In 1989, with less than 20% of black students, HBCUs awarded 40% of all black B.S. degrees in natural science, according to the National Science Foundation (NSF). At the bachelor's level, the top five producers of black biologists are all historically black schools (see table on page 1218).

And graduates from many of these schools go on to make the grade in Ph.D. programs at mainstream universities, suggesting that at least some HBCUs offer a good grounding in science. For example, of the roughly 700 blacks who received a Ph.D. in science and engineering between 1986 and 1988, 29% earned their bachelor's degree at a black college, according to NSF. In some fields the figure was much higher: 42% of black Ph.D. biologists and 36% of black Ph.D. engineers received undergraduate degrees from black schools.

Fans of the HBCUs say the numbers reflect what they do best: teach undergrads. Students are routinely showered with personal attention. At Clark Atlanta University, for example, biology professor Isabella Finkelstein keeps track of the academic profiles of students in her class. "I see a kid with 1200 SAT scores who gets a 30 on my first test, I put a note on there: 'YOU CAN DO BETTER.'"

Psychological boost. Black colleges' chief advantage--an environment that nurtures self-confidence--is hard to measure. But most HBCU grads insist the advantage is there. They say that at mostly white schools, simply being in the minority exacts a psychological toll. Spelman grad Sharon Neal, now assistant professor of chemistry at the University of California, Riverside, attended a white prep school in Philadelphia. The school "did more for me intellectually than any other experience," she says. "But it was at a great personal price in my youth. I got so sick of people being your friend in school and then not knowing you when we met in a department store." Other graduates of white high schools remember never getting dates and feeling pressure to live up to stereotypes like knowing the latest dance steps. Neal turned to Spelman because she wanted a place where "race just wasn't an issue."

Such social concerns may seem irrelevant to what ought to be a primary concern in college: making the grade. But when blacks--or any other group--are in the minority in school, they tend to work in isolation. And in tough science courses, the savvy strategy is to band together. "The minute I didn't understand something in biochemistry the first thought in my head was, 'I'm the only one who doesn't understand this,'" remembers NSF's Johnson. "It took group study to realize the other guys didn't understand it either."

Working in concert with classmates is key, agrees mathematician Gloria Gilmer, who runs an educational consulting company in Milwaukee, Wisconsin, and has taught at six HBCUs as well as several mostly white universities. "I tell students to go where they give Ph.D.s to people who look like you. Don't go to some school and sit in a class where you're not even taking the same course as the rest because you're isolated and they're working together."

And at majority schools, the lone black chemistry major may feel that his every move must prove that black people can make it. The pressure not to make mistakes is huge. "People forget that freshmen are 18-year-olds. They're still kids," says Johnson. "They need to be able to be young, and do silly, foolish

things, and not be under a microscope."

Working alone makes hard problems nearly impossible; maybe that's part of the reason blacks at majority schools tend to drop out of tough hard science courses and major in "softer" social sciences. Mainstream universities enrolled about 80% of black students and produced 74% of the black B.S. social scientists in 1989--and only 63% of the computer scientists, according to NSF.

Walter Pattillo Jr., chair of the biology department at historically black North Carolina Central University, complains: "The way we see it, the majority schools are wasting large numbers of good students. They have black students with admissions statistics that are very high, tops. But these students wind up majoring in sociology or recreation or get wiped out altogether." As a result, Pattillo is somewhat skeptical of majority schools who come calling: "These white schools come here asking for graduate students, and we say, 'What are you doing with the students you already have?' One of my colleagues says they got the cream, now they come back for the skim milk."

Coddling students? Others, however, point out the dangers of coddling students. Campuses devoted to nurturing may not be as academically rigorous as majority universities that expect students to "sink or swim." Upon arriving as an assistant professor at a well-regarded HBCU about 10 years ago, one black scientist recalls thinking that the school was more like a high school or junior college than a university. Professors were expected to call the roll before each class.

And students at black schools may be inadequately exposed to the research world: "Science is a culture," says Bertram Fraser-Reid, a Jamaican-born black chemistry professor at Duke. In his lab, he says, undergrads soak up chemistry simply by socializing with grad students and postdocs. If you choose a black or inexpensive private college, says Fraser-Reid, "You may be gaining one culture at the expense of the other."

In science, a good undergraduate education means research, or at least some ambitious lab courses--and that takes money. Financially strapped HBCUs may not be able to provide those courses. "Undergraduate teaching in science is an extraordinarily expensive business. People these days can't learn about molecular modeling, they need to learn how to do it," says Fraser-Reid.

At Pattillo's university, North Carolina Central University in Durham, for example, students--including master's students--had no access to many of the tools of modern molecular biology. Only last year, after one young faculty member won outside funding for a new lab course, did the university offer training in cloning, the polymerase chain reaction, and other basics.

This has long been a problem at black colleges. "I was poorly prepared," says Kenneth Olden, director of the National Institute for Environmental Health Sciences, who got his B.S. from Knoxville College in 1960. "I learned science from a descriptive point of view. I wasn't very quantitative. I hadn't done much lab work." As a result, Olden now believes that for many minority students, major universities are the way to go. "When you really get down to it, if you say, 'What I really want for my child is a serious rigorous academic training,' then you're probably talking about a majority school."

Tradeoff. Maybe the best solution, some say, is an education that combines the best of both worlds. Says Meredith Williams, a Yale-educated young physicist, now in grad school at North Carolina State University, a majority school, "In my dream world I'd go to an HBCU for 2 years and then transfer to Yale. Because I've seen how people come out of those black schools. They exude the message, 'I'm capable.'"

The ability of black colleges to keep turning out such confident students, however, will depend on whether they can continue to recruit outstanding faculty. Thirty years ago, that task was easy: All top black scientists went to schools like Howard and Tuskegee, since they were unwelcome elsewhere. No longer. Many HBCU fans worry that their faculty ranks are filling with foreign professors, instead of minority role models. And in the long run, HBCUs will have to rely on more than a sense of commitment to attract faculty.

For example, Stackhouse, who received three degrees from black schools, now teaches at one, Winston-Salem State University. "If we don't return to minority institutions, who will?" he asks. He keeps a research connection alive through summer programs but wonders if that will be enough. In his own university, he's frustrated by heavy teaching loads and lack of lab space and equipment. But like many black college alumni, he is passionate about keeping black schools alive so students have a choice. In his view, until integration works in both spirit and practice, some black students will benefit from learning science in a place where, for a few years at least, they are the majority.

GRAPHIC: Photograph; Table

IAC-NUMBER: IAC 13217814

IAC-CLASS: Magazine

LANGUAGE: ENGLISH

LOAD-DATE: August 28, 1995

March, 1994

SECTION: Vol. 24 ; No. 2 ; Pg. 6; ISSN: 0093-0334

LENGTH: 8311 words

HEADLINE: The question of human cloning.

BYLINE: Robertson, John A.

BODY:

Accustomed though we are to advances in medical technology, a 24 October 1993 news report that human embryos had been cloned astonished many persons. A New York Times story, "Researcher Clones Embryos of Humans in Fertility Effort," was the feature that Sunday morning in many newspapers throughout the country. Media coverage continued for several days, with debates about cloning on editorial pages, Nightline, and Larry King Live.

Within a week the issue had faded from media consciousness, aided in part by Time and Newsweek stories that stressed the huge gap between die reported research and the Jurassic Park-type fears of cloned human beings that initially spurred national coverage. Bioethicists and law makers, however, must still contend with the ethical and policy issues that even limited cloning of humans presents. Should researchers be free to continue cloning research? May infertile couples and their physicians employ cloning to form families? Or should government prevent cloning research or discourage some or all of its later applications?

As with many biomedical developments, these questions present a mix of issues that need careful sorting. They involve, among others, questions of the propriety of embryo research, the validity of deliberately creating twins, and the importance of nature versus nurture in forming human beings. They also raise slippery slope concerns: should otherwise seemingly valid uses of a new technique be stopped to prevent later undesirable uses from occurring? To address those issues we must first describe the cloning research that has touched off the furor and the concerns that it presents.

Two Types of Cloning

The research that put cloning on the public agenda was a long way from Huxleyian fantasies of identical babies, mass produced in laboratories, and did not involve cloning as conventionally understood at all. To clone means to create a genetic copy or replica. Perhaps due to science fiction fantasies, it has been assumed that cloning would occur by removing the nucleus from the cell of one person, placing it in an egg that has had its nucleus removed, and then implanting it in a laboratory incubator or a woman who would bring to term a child with the identical genetic characteristics of the person providing the cell nucleus. Although this procedure has worked with frogs, it has never succeeded with mammals and appears highly unlikely to be accomplished in even the mid-range future. If this form of cloning were possible, scientists could

fabricate as many copies as one wished of any available human genome, subject only to the limits of uterine or artificial gestation.

A second and more limited way to create clones is to split the cells or blastomeres of an early multicelled embryo before the cells have begun to differentiate. Because each blastomere at this stage is in theory totipotent (that is, capable of producing an entire organism itself), die separated cells can become new embryos, all of which which have the same genome. This form of cloning is now practiced to some extent in the cattle industry. Cloning by blastomere separation is limited to the number of cells that can be separated before cell differentiation, which destroys totipotency, occurs.

The study that generated the recent interest in cloning involved a small but essential step toward cloning human beings by embryo splitting. Researchers at George Washington University Hospital in Washington, D.C., separated cells or blastomeres from seventeen two- to eight-celled preembryos and showed that, to a limited extent, they would divide and grow in culture. The cells had been obtained from polyspermic embryos that had no chance of implanting in the uterus and that ordinarily would have been discarded.

The separated blastomeres were coated with an artificial zona pellucida and placed in the culture medium used for in vitro fertilization (IVF).

The researchers obtained forty-eight blastomeres from the seventeen polyspermic embryos (eight two-cell, two three-cell, five four-cell, and two eight-cell), or theoretically forty-eight new totipotent embryos. A similar percentage of embryos cleaved for each stage of the embryo from which they were taken. While morulas (thirty-two-celled embryos) were achieved when blastomeres from two-celled embryos were cultured, blastomeres from four-celled embryos developed only to the sixteen-cell state, and no blastomeres derived from the eight-cell stage grew past eight cells in culture. These results suggest that splitting embryos at the two-cell stage appears to be more conducive to further development than does separation at the four-cell or eight-cell stage. However, the maximum stage at which a single blastomere can be reprogrammed to exhibit totipotency by itself or with cellular materials transplanted from other cells is unknown. 2

The study thus demonstrated that experimental cloning or twinning of human embryos is potentially feasible as an aid to relieving infertility, though much additional work remains before offspring are produced, and there is uncertainty whether the technique will ever work at all. To produce a child by this method would first require showing that excised blastomeres from normal embryos would grow in culture to the point at which transfer to the uterus would ordinarily occur. Such research should also show the optimal stage for splitting normal embryos. It would then be necessary to place embryos that appear to be developing normally from split blastomeres into the uterus to show their potential for implantation and a successful pregnancy.

Some experts, however, are dubious that infertile couples would ever benefit from cloning by blastomere separation.3 They view the higher pregnancy rate after transfer of several embryos as due to the genetic heterogeneity of the embryos transferred, not to numbers alone. On this view, placing several genetically identical embryos in the uterus will not increase the chances of pregnancy if one embryo with that genome would not have implanted. If this view is correct, there will be little incentive to use blastomere separation to

treat infertility, and the ethical issues discussed below will have little practical significance. The following discussion, however, assumes that blastomere separation could provide certain advantages in treating infertility, and examines the ethical and policy issues that then arise.

Fears and Concerns

Some commentators saw nothing particularly unethical or disturbing in the George Washington research. This was simply another step toward improving the efficacy and efficiency of IVF, particularly for those couples who produce too few eggs or embryos to initiate pregnancy.

Many news reports, however, highlighted the disturbing or possibly unethical features of cloning and quoted ethicists who found the practice troubling. They described hypothetical scenarios in which embryos would be cloned for sale or to produce organs and tissue for existing children who needed transplants. One ethicist termed cloning as "contrary to human values"; others saw it as "an opportunity for mischief " that called for "governmental and societal debate and, perhaps, prohibitions and restraints." 4 The Vatican newspaper termed it a step into "a tunnel of madness," while the United Methodist Church called for an executive order banning cloning in all federally financed institution. 5 A poll a week after the first story reported that 60 percent of Americans opposed cloning. 6

The fears and concerns about cloning have several strands. Some of them arise from the artificial nature of assisted laboratory reproduction. Others are tied to discomfort with the manipulation and destruction of embryos that cloning research, if not the procedure itself, will inevitably cause. The most prevalent ethical concern, however, arises from the dangers that intentional creation of identical twins or multiples of one genome might pose to resulting offspring. The fear is that cloning will violate the inherent uniqueness and dignity of individuals, as well as create unrealistic parental expectations for their children. It also opens the door to identical embryos being created and sold because of their genetic desirability, as cattle embryos now are sold to increase animal yield and profitability. A worst-case scenario envisages the mass production of identical embryos to be sold to persons seeking desirable children. Finally, there are fears that embryos will be created to provide organs and tissue for existing children who need transplants.

Despite these reservations, research into the feasibility of splitting embryos will undoubtedly continue. Cloning by blastomere separation is basically a mechanical procedure that requires only the ability to micromanipulate fertilized eggs and embryos and a few hundred dollars' worth of culture medium. 7 No DNA analysis or genetic expertise is necessary. It is likely that the next research steps - separating and culturing single blastomeres from normal embryos and then placing those that grow well into the uterus - and the actual birth of children as a result of embryo splitting might well occur in the next two to five years. As micro- manipulation of eggs and embryos is a rapidly growing practice, the ability to excise blastomeres from an embryo will easily be within the reach of many IVF physicians and embryologists. If shown to be safe and effective, physicians in many fertility centers will then offer the procedure to patients.

These possibilities engender a recurring disquietude about new reproductive technologies. Scientific zeal and the profit motive combine with the desire of

infertile couples for biologic offspring to create an enormous power to manipulate the earliest stages of human life in infertility centers across the country. Even before one innovation is fully assimilated, the largely unregulated billion-dollar infertility industry presents another improvement,' which separately or together threatens disturbing consequences for offspring, families, and society.

Some persons would argue that the idea of creating exact replicas of other human beings is so novel that there should be a moratorium on further research and development until a national consultative body evaluates the ethical acceptability of the procedure and develops guidelines for research and use of the technique. At the very least, to prevent abuses there should be strict rules about the circumstances in which cloning by embryo splitting occurs, and about the uses made of cloned embryos.

A closer look at the issues, however, suggests that the most likely uses of cloning are neither so harmful nor so novel that all research and development should now stop until the ethics of the practice are fully aired, or that governmental restrictions on cloning research or applications are needed. Indeed, there may be no particular need for guidelines beyond the full and accurate disclosure of risks and success rates that should always occur in assisted reproduction.

To assess the ethics of embryo splitting and the need for regulation, we must first ask who would use this technique if it were available and why, and then analyze the ethical issues that the likely demand for cloning would generate. We can then address the need for regulation of the embryo research that is essential if cloning by blastomere separation is to occur, and of the uses to which cloning techniques will be put.

The Demand for Cloning

The news accounts of the George Washington University research emphasized many speculative uses of cloning, thereby slighting the most likely uses of the technique. The immediate impetus to develop cloning - and its most likely future use - is to enable infertile couples going through IVF to have a child.

To Increase the Number of Embryos Transferred. Initially the main demand for embryo splitting would come from couples undergoing IVF who cannot produce enough viable embryos to initiate pregnancy. In basic IVF practice, the highest rates of pregnancy occur with transfer of three to four embryos. Often more than that number of eggs has to be fertilized to produce enough viable embryos for transfer, with the excess frozen for use during a later cycle. Couples who produce only one or two embryos may thus have undergone an expensive and, for the woman, onerous procedure that has little chance of success.

Cloning by blastomere separation appears to be a reasonable step for such couples, if genetic heterogeneity of transferred embryos turns out not to be a key determinant of pregnancy success rates. Their goal is the birth of at least one child. If the prospective parents produce only two embryos, they would face the difficult choice of transferring those two in the hopes that a single pregnancy would result, or increasing their chances of having one child by splitting the blastomeres of one or both embryos.

If they produce only one embryo and embryo splitting has been shown to be safe and effective, they may opt to divide that embryo. Depending on the embryonic stage at which splitting is most successful, this could produce two embryos (if split at die two-cell stage), four (if split at the four-cell stage), or even eight (if two embryos are both split at the four-cell stage).

The number of embryos they end up with will affect the number of embryos placed in the uterus at any one time, and also whether cloned embryos remain available for transfer on a later cycle. If their efforts yield only two embryos, it is likely that both will be transferred to the uterus. (If both implant and come to term, embryo splitting will have produced identical twins).

If they produce four or more viable embryos by blastomere separation, three or four might then be transferred to the uterus in the hopes of having one child, with the rest frozen for later use. 8 Assuming two cycles of transfer with two to four embryos transferred in a given cycle, several possibilities arise. No children could be born from transfer in either cycle, or one or two could be born from the first transfer, and none from the second, or vice versa. In any given case, no child, one child, or deliberately created twins would have been born as a result of blastomere separation.

However, this scenario also opens the door to having "twins" (or even triplets" or "quadruplets") born several years apart. This would occur if one or two children were born as a result of the first transfer cycle. Three years later, perhaps, the couple wishes to have a second child, and rather than go through IVF again, opts to have the remaining cloned embryos thawed and transferred to the wife's uterus. The period between births of children with the same genome could vary from a year or two to several years.

Embryo Splitting to Avoid Subsequent Egg Retrieval. Other scenarios involving embryo splitting as a treatment for infertility can also be envisaged. Perhaps the next most likely scenario if cloning by blastomere separation is in fact effective would arise with a couple undergoing IVF who produce a sufficient complement of viable embryos to initiate a pregnancy - three or four - but who wish to avoid the expense and burdens of subsequent egg retrieval cycles. Not many IVF candidates are likely to find themselves in this position, since ovarian stimulation often produces ten or more eggs. Because the couple would need to splitt only one or two of the three or four viable embryos that they have produced, it is conceivable that many couples who produce only four embryos would opt for this procedure. Indeed, the demand for embryo splitting from this group might arise even if it turned out that successful implantation requires genetic heterogeneity of embryos and the procedure thus was not sought by the group that produces very few eggs.

If some of their embryos are split but only noncloned embryos are transferred during the first or subsequent cycles, couples may satisfy their need for offspring without having to resort to cloned embryos. However, if uncloned embryos do not produce (enough) children, some of the cloned embryos may be thawed and transferred during a later cycle. In that case deliberately created twins could result at the same time, or at a point separated in time from the first child born with that genome. A third or fourth cycle using cloned embryos could result, with genetic replicas of earlier children born separated in time.

In either scenario, cloned embryos that are no longer needed by the couple that produced them might be discarded or donated to other infertile couples. Twins or triplets of an existing child might then be born to and reared by another couple. Because embryo donation is ordinarily anonymous, neither the children nor the genetic or rearing parents are likely to know the identity of the others.

Embryo Splitting as a Form of Life or Health Insurance. An often cited though highly unlikely demand for embryo cloning could arise from couples seeking insurance against disaster for any children that they have. That is, a couple might request that one or more blastomeres be split from embryos that will be transferred, so that the resulting clone can be frozen for later use in case the child born from the source embryo later dies or needs an organ or tissue transplant. In that case, embryos that are genetically identical to the child already born can be thawed and implanted in the mother (or a surrogate) to produce a genetically identical child to replace the dead child, or to serve as an organ or tissue donor for an existing child.

This scenario could occur, but it is unlikely for several reasons. First, few couples not otherwise undergoing IVF would choose to do so just to gain the hypothetical protection that identical backup embryos might provide. Second, couples that experience the death of a child may not, because of the sadness that it will engender, want to replace that child with a genetic twin, much less plan even before the first child is born to create a replica for that purpose. Third, couples undergoing IVF who produce enough embryos for transfer may not want to risk their viability by separating blastomeres for hypothetical insurance purposes. Fourth, a genetic replica of an existing child might not be necessary to provide needed organs or tissue, or there may not be sufficient time once organ failure in a child occurs to thaw, implant, and bring to term the cloned embryo to serve as an organ or tissue donor. Fifth, there may be medical reasons why a genetic twin will not be suitable as a donor, though in some cases, such as bone marrow or kidney transplantation, genetic homogeneity could provide an advantage.

Because so few couples - even those otherwise going through IVF - will request embryo splitting for this purpose, the use of cloned embryos as backup protection for existing children is likely to arise only with embryos that were created to enhance the efficiency of IVF. In situations of this kind, where the embryonic clones were not produced with the specific intention of insuring against disaster, parents might occasionally be glad of the opportunity to avail themselves of the stored cloned embryos to obtain tissue for transplant for an existing child, or to replace a child who has already died. Such scenarios are not impossible, but for the reasons stated above, they are not likely to be frequent.

Embryo Splitting to Obtain a Desirable Genome. Ethicists have speculated that cloning by embryo splitting might occur to facilitate, or might result in, the selection of stored embryos deemed to be particularly desirable. They envisage scenarios whereby parents will try to sell clones of desirable children to other couples, or where an attractive or successful couple will clone many embryos for later sale or dissemination.

These speculations are highly fanciful. Most couples are not in the market for other peoples' genetic offspring, but prefer to have their own. If so, they can exercise some control over the genetic characteristics of offspring by

mate or gamete selection, or by preimplantation or prenatal genetic analysis. Few couples who can have their own children would be so obsessed with having a perfect child that they would eschew their own reproduction in order to obtain a cloned embryo that appears to have a desirable genome.

Of course, if cloning by embryo splitting is perfected, one could routinely excise and store a cell from every embryo that is produced and transferred to the uterus (assuming that this will not impair the embryo's development). The children born of the source embryo could then be followed, and the excised cells of those that turn out to have good genomes or healthy lives might then be sought by persons in quest of donor embryos. The mere description of the procedure shows how complicated and unwieldy it would be as a means to produce particularly desirable embryos.

However, couples who cannot produce genetic offspring might wish to have some say in the characteristics of embryos donated to them. In addition to choice of hair and eye color, and assurances that there are no genetic defects, they might want to see what the embryo they choose would look like as a child or youth, if such information were available. But there is no particular reason why it would be available, or why it would necessarily have to be provided.

In any event, providing information about cloned embryos to prospective recipients would not itself lead to embryo splitting specifically for purposes of genetic selection. The couple undergoing IVF might clone to enhance IVF efficiency, but there would be no particular point in cloning embryos just to enable genetic selection of donor embryos to occur at some later time. If the sale of embryos is also prohibited, the financial incentives necessary to induce embryo splitting for later sale would not exist.

Ethical Issues: Destruction of

Embryos

Cloning by blastomere separation raises a number of ethical issues. Some ethical concerns derive from the stark interference with natural reproduction, or the manipulation and destruction of embryos that cloning necessarily entails. However, those concerns are not unique to cloning, and have been voiced about embryo research, freezing, and discard, and about IVF generally. Since they are not deemed sufficient to justify banning or restricting those accepted forms of assisted reproduction, they should not be sufficient to ban cloning either.

Yet persons who believe that fertilized eggs and embryos are already persons with rights will object that embryo splitting goes beyond the manipulations ordinarily involved in IVF. In this case a new unique individual will be intentionally split to serve other ends. The very process of blastomere separation could destroy embryos that would have developed normally, thus denigrating and undermining the value of human life. Because human life at all stages is a preeminent value, cloning by blastomere separation is an unethical procedure that should be banned.

There may be no way to answer the objections of persons who think that embryos are themselves persons and must be protected at all costs. The fact that embryo cloning might yield additional human lives will not assuage their concerns, for one is ordinarily not justified in killing one person in order to save several. 9 One can only point to the prevailing moral and legal consensus

that views early embryos as too rudimentary in neurological development to have interests or rights. 10 On this view, splitting embryos can no more harm them than freezing or discarding them can. Nor is splitting embryos to enable one or more of them to implant and come to term inherently degrading or disrespectful of human life. Cloning embryos thus poses no greater harm to embryos than other IVF practices and should be permitted to the same extent that they are.

Ethical Issues: Deliberate Twinning

Ethical objections that are unique to cloning arise from a concern that the intentional creation of genetic replicas of an existing person denies the uniqueness of resulting offspring. This could occur from causing more than one child with the same genome to be born simultaneously. It could also occur from causing more than one child with the same genome to be born at different points in time.

Is the intentional creation of twins who are born simultaneously morally objectionable? Identical twinning occurs naturally and is not generally thought to be harmful or disadvantageous to twins. If anything, being a twin appears to create close emotional bonds that confer special advantages. If this is true, then having twins as a result of embryo splitting should be no more harmful to offspring than having twins naturally.

Suppose, however, that having twins does sometimes pose rearing problems or even psychological conflicts for children. For example, some families may have trouble rearing two infants simultaneously. Or asymmetrical relations with parents or intense rivalry between twins may occur, resulting in psychological harm to one or both of the pair. Still, the fact that undesirable outcomes might occur for some twins is no basis for concluding that all embryo splitting is unethical and should be discouraged.

The greatest chance that twins would result from embryo splitting would arise with a couple who produce too few embryos to have a reasonable chance of establishing even a single pregnancy. Their goal in embryo splitting is to have one child (or sometimes possibly two), but they know there is the risk that a twin pregnancy will result. If they knowingly accept the risks of twins, they will most likely be in a good position to handle the special burdens posed in rearing them. In any event, the risk of psychological harm from being a twin is neither so likely nor so severe that merely being born in this situation could constitute a harm. Twinning, whether natural or intentional, hardly amounts to a wrongful life. Neither child can reasonably claim that she has been wronged because, but for her parents' choice, she would have been born without a twin.

What, however, if triplets or even quadruplets are born simultaneously as a result of cloning by blastomere separation? If a four-cell embryo is split into four, and all separated blastomeres grow in culture and then are placed simultaneously in the uterus, the risk of a multifetal pregnancy increases. Multiple gestation does pose physical risks to the mother and to fetuses. Thus women who have multifetal pregnancies as a result of IVF or fertility drugs often use selective abortion to reduce the pregnancy to twins or triplets to improve the chances of a healthy outcome for all concerned. If multifetal pregnancies due to cloning occur, it is likely that they will also be selectively reduced to protect the health of mother and offspring.

Suppose a woman who is pregnant with triplets or quadruplets in virtue of transfer of four cloned embryos refuses to reduce the pregnancy to twins. Will she harm her offspring as a direct result of the cloning decision? Two different harms must be distinguished here. One is the potential harm of having three or four genetically identical siblings rather than just one, as occurs with twins. The second is the physical harm from prematurity that all offspring in such a multiple gestation might experience.

With regard to the first harm, it is not at all clear that identical triplets (or rarely, even quadruplets) suffer unique or inordinate psychological problems because they have identical siblings. If being an identical twin is generally a good thing, then it may be that being an identical triplet also has advantages and specialness that outweigh whatever disadvantages exist. At the very least, it would appear difficult to argue that these disadvantages are so great that the triplet should never have been born. Given that this is the only way for this individual to be born, its birth hardly appears to be a wrongful life that never should have occurred.

The risk of physical dangers of prematurity from a triple (or quadruple) pregnancy raises somewhat more complicated questions. Suppose the pregnancy ends prematurely at seven months. All three infants spend several weeks in intensive care and end up with permanent learning and physical disabilities. Have they been harmed by the cloning that produced a multifetal pregnancy, which their mother refused to reduce to twins? The child who would have been aborted would not appear to have been wronged by the mother's refusal because it had no other way of being born but in a triplet situation subject to the very risks that have eventuated.

But two of the three infants (there is no way to identify the two that would not have been aborted) are worse off than they would have been if the pregnancy had been reduced to twins. Presumably they would then have been born healthy, without the physical and mental deficits they now have. One could reasonably argue that they have been hurt by their mother's refusal to reduce the pregnancy, even though there is no way to tell which two they are.

If the disabled offspring have been wronged, the wrong is not due to embryo splitting but rather to their mother's refusal to reduce the pregnancy from triplets to twins. The same arguable wrong would occur if the triple pregnancy occurred naturally or as a result of assisted reproductive techniques that did not involve cloning. Because the possibility of this wrong to the injured offspring is not unique to cloning, it is not an argument against all embryo splitting, any more than it is an argument against all use of fertility drugs or IVF, which also can produce multifetal pregnancies that are not reduced.

Ethical Issues: Later Born Twins

The second ethical issue unique to cloning by embryo splitting is the possibility of genetically identical siblings being born years apart in the same or different families. Are later born children harmed because a twin or triplet already exists? The claim rests on the notion that the later born child lacks the uniqueness or individuality that we deem essential to human worth and dignity, and that human individuality is largely determined by nature or genome rather than by nurture and environmental factors. Because phenotype and genotype do diverge, and because the environment in which the child will be raised will be different from that of his older twin, the child will still have a unique

individuality. Physical characteristics alone do not define individuals, and there is no reason to think that personal identity will be wholly controlled by having an older twin.

Still, there could be special problems faced by such a child. Its path through life might be difficulty if the later born child is seen merely as a replica of the first and is expected to develop and show the skills and traits of the first. This might be a special danger if the later born child is used as a replacement for an earlier born child who has died. However, it will be some years before the later born child is even aware of his genetic identity relative to an older sibling and the special expectations his parents might have.

But it is also as likely that the later born child will be loved and wanted for his own sake. His status as a later born twin (or triplet) could be seen as a special status, indeed, a unique or novel status that confers attention and love. It could also lead to close ties with the older twin, if the special bond that twins feel is genetically based. However, it could also lead to unique forms of sibling rivalry. Will the older twin feel that he is deficient because his parents wanted a newer version of him, or will he feel special and proud that his parents wanted another child like him? In any event, it is difficult to conclude that later or earlier born twins or triplets are likely to have such serious psychological problems that they should never be born at all. Even if one did so conclude, this would counsel against implanting cloned embryos only when a twin already exists, not against implanting two cloned embryos simultaneously or splitting embryos at all.

Ethical Issues: Cloning as Life or

Health Insurance

Although cloning for the explicit purpose of providing parents with a replica for a lost child or as a source of organs or tissue for transplant for an earlier born child will not frequently occur, couples who have split embryos to treat infertility might occasionally be faced with thawing a cloned embryo for those purposes. Consider, for example, parents who request cloning to protect against the loss or death of a child, or who wish to thaw a cloned embryo to replace a dead child. Wanting a child to replace one who has died is not itself unethical. Nor does it become so merely because the new child will be a twin of the first. Although the parents may hope that the new child will develop and show the same traits as her deceased twin, they should very rapidly learn that the second child is different in some respects and similar in others, and would ordinarily come to treat and accept her as the individual that she is.

The use of cloned embryos as insurance against organ and tissue failure in an existing child presents a different set of issues. Here the concern is that the cloned embryo will be treated as an instrument or means to serve the needs of an older twin and will not be loved or respected for his own sake. As the Ayala case in California showed, however, a family can be motivated to have another child to provide an existing child with bone marrow and still treat the subsequent child with the love and respect that children deserve.

If this is so, thawing cloned embryos to provide tissue or organs for an existing child should also be ethically acceptable. The key is whether the child will be loved and accepted by the family that brings her into the world, not how or why she was conceived, nor even whether she was cloned for that purpose. As

long as the child's interests are protected after birth occurs, it is hard to see how being cloned or thawed to provide organs for a twin is any worse than being conceived for that purpose. Even if it were, the risk that some cloned embryos might be used to provide tissue to existing children would not justify a ban on embryo splitting to treat infertility.

Ethical Issues: Embryo Splitting for Genetic Selection

Scenarios involving embryo splitting for genetic selection are, as discussed above, extremely unlikely as long as overall demand for embryo donation is low and the buying and selling of embryos is not permitted. Since it is highly unlikely that a market in embryos will develop, there will be little incentive for couples going through IVF to clone embryos in order to sell them in the future. This is true even if recipients of donated embryos are permitted to pay some of the costs of embryo production.

It is true that the small subset of infertile couples who are candidates for embryo donation might wish to know the actual characteristics of existing twins or triplets of the embryos they seek to "adopt." However, neither having nor satisfying this wish is itself immoral. Indeed, the right of adoptive parents to receive as full information as possible about the children whom they seek to adopt is increasingly recognized. There is no reason why the same principle should not apply to embryo "adoptions." Even though the couple seeking the embryos will be choosing them on the basis of expected characteristics, such a choice is neither invalid nor immoral. As long as the parents are realistic about what the information signifies, do not have unrealistic expectations about the child's perfection, and love the child for itself, seeking and providing such information prior to embryo donation should be ethically acceptable. If it were not, providing such information could be banned without requiring that embryo splitting to treat infertility also be banned.

Regulatory Issues

This account of cloning by embryo splitting and the ethical issues it poses suggests that, contrary to initial impressions, there is no major ethical barrier to proceeding with further research in embryo splitting as a treatment or adjunct to IVF. Given the great utility that embryo splitting could have for infertile couples, a moratorium on embryo splitting research is both unnecessary and unjustified. Such moratoria have occurred only when research appeared to pose great danger to others, as occurred with the brief moratorium on recombinant DNA research declared at Asilomar in 1975 because of the fear that genetically engineered pathogens might escape from the laboratory. By contrast the risks of embryo splitting are no different from the risks that now exist in IVF laboratories and should be treated accordingly.

Even if a moratorium on cloning research is not justified, persons leery of embryo splitting argue for close regulation of the research that could perfect the practice, and then of its application. The most immediate policy questions concern whether there should be any restriction on research with embryos designed to improve or perfect techniques of embryo splitting. If research establishes the safety and efficacy of embryo splitting, then the question of regulatory limits on the use of the technique must be addressed.

The issue concerning the ethics of embryo research has several parts. One is whether research on normal embryos that will otherwise be discarded is ethically acceptable for any purpose. The second is whether embryos created by splitting blastomeres may ethically be placed in the uterus and brought to term. Such questions should be answered in terms of risks to the human subjects directly involved. As we have seen, the use of cloned embryos to treat infertility appears to be ethically acceptable. One should not deny investigators the right to carry out research otherwise respectful of human subjects because one disagrees with the utility or worth of eventual applications.

Research with Normal Embryos.

The most immediate question is whether researchers should be permitted to split and culture blastomeres from normal embryos in order to replicate the results obtained at George Washington with polyspermic embryos. Although no authoritative American guidelines exist for research on normal embryos, there is a strong basis in the ethical literature and in practices of other countries for holding that such research is ethically acceptable. 11 Because early preimplantation embryos have no differentiated organs or nervous system, they cannot be harmed by splitting or other research manipulations and thus may ethically be used as the objects or vehicles of medical research.

As long as the research is for a valid scientific purpose, embryos that would otherwise be discarded can, with the informed consent of the couple whose gametes produced the embryos, ethically be used in research. Indeed, it should also be ethically acceptable to create embryos solely for research purposes when needed, even if there is no intent to place them in the uterus. Thus neither the lack of guidelines, the moral objections of some to any embryo research, or fears about where cloning research might lead justify forbidding researchers to take this next step. Researchers may not have the right to receive governmental or private funds for cloning, but if they are otherwise funded, their research should not be stopped because of objections to the use of embryos or to cloning itself.

Embryo Transfer after Splitting.

Harder questions will arise if research shows that blastomeres separated from healthy embryos develop normally in culture to the point where they may implant in the uterus and go to term. Universities and IRBs might legitimately demand that implantation of manipulated embryos not occur until there are reasonable assurances that resulting offspring will not be physically harmed by the experiment. But if the embryos have developed normally in culture, this condition should be satisfied, just as it has been with embryos that were experimentally frozen and thawed before transfer, and with embryos that have been experimentally biopsied for preimplantation genetic analysis. When no physical harm appears likely, transfer to the uterus is ultimately beneficial for the resulting child (who has no other way to be born) and should be permitted. Again, neither the lack of clear guidelines, the fact that embryos will be manipulated and transferred, nor speculative fears of where blastomere separation ultimately could lead would be valid grounds for blocking this research.

Such a conclusion is consistent with the recommendations of commissions and advisory boards in the United States and abroad that have examined embryo research. Although they have not addressed cloning research directly, they do

approve of transfer of embryos to the uterus after experimentation when the research is designed to aid or treat the resulting child. Transfer after experimental embryo splitting is designed to enable a child produced from blastomere separation to be born, and thus might be said to advance its interests. Just as the first embryo transfers after IVF were ethically acceptable because they enabled children to be born, so these should be as well, for there is no reason to think that if they implant and come to term they will have physical defects or otherwise be harmed.

Embryo Splitting Applications.

Once it is shown that embryo splitting can produce normal offspring, the relative ease of the procedure and competition for parents will lead many IVF centers to offer it. Will it be necessary to restrict the uses to which embryo splitting is then put?

As the previous analysis suggests, the case for banning or greatly restricting embryo splitting as a treatment for infertility is extremely weak. The right of married and arguably even unmarried persons to procreate is a fundamental constitutional right that cannot be restricted unless clearly necessary to protect compelling state interests. 12 Because a ban on embryo splitting to treat infertility would directly interfere with the ability of infertile couples to have offspring, it would have to meet the compelling interest standard. Yet the prospect of great harm from intentional twinning, from twins born years apart, or from other possible uses of the technology does not appear to be so likely that governmental restrictions that go beyond assuring informed consent could be justified.

As with other forms of assisted reproduction, medical professionals who offer the service may be left largely to regulate themselves. IVF programs that engage in embryo splitting will have to decide at what stage embryos will be split, how many clones will be made, how many will be transferred at any one time, and how great a gap in time may, occur between the birth of one child and another whose origin was the same embryo. They mill have to develop procedures for counseling couples, particularly when twins are born months or years apart. Professional organizations, such as the American Fertility Society, might develop practice guidelines, as they have done with donor sperm and other reproductive technologies. 13 As long as the interests of couples and offspring are well served, there will be no need for governmental restrictions on the decisions made by medical professionals and their patients.

Nor do the more exotic scenarios imagined with cloned embryos necessarily warrant governmental intervention. The use of cloned embryos to replace a lost child or to provide tissue or organs for an existing child should be decided on the merits and ethics of those practices independently of creating or using cloned embryos for those purposes. If families may otherwise have children to serve as tissue donors for existing children, there is no basis for banning the use of cloned embryos for that purpose. Such uses are likely to be rare, and in any event, should not stop the use of cloning to treat infertility.

Similarly, couples seeking embryo donations should be entitled to as much information about the genetic characteristics of prospective offspring as is available. Wanting healthy, talented, attractive children is not per se immoral and should not in itself bar the use of the technique. Of course if it did, that would not bar other uses of cloned embryos.

Laws that restricted trade or commerce in cloned embryos would be an acceptable public policy. Athough it is highly unlikely that demand for cloned embryos would lead to a market in them, it may be desirable to symbolize the unique value of incipient human life by banning the sale of embryos, whether cloned or not. Such a ban would not prevent infertile couples from getting access to infertility treatments or otherwise forming families, and thus would not limit or interfere with their procreative liberty. The ban need not prevent persons receiving embryo donations from sharing in some of the costs of embryo production.

The Permissibility of Cloning

The idea of cloning human beings initially sounds so bizarre and dangerous that one would think that such practices should be closely regulated, if permitted at all. Yet this survey of ethical and policy issues in cloning by embryo splitting suggests that the procedure has fewer risks and more benefits than first appeared and would be ethically permissible in most cases. The most unappealing appealing applications of the technique are highly speculative and could be restricted without also stopping more valid uses.

Cloning by embryo splitting thus presents a regulatory situation that often arises with new reproductive technologies. An immediate step that seems justified to meet the legitimate needs of infertile couples could open the door to future applications that are much less defensible. If we ban the immediate steps in order to prevent potentially harmful future applications, infertile couples lose the benefits of the procedure without a clear showing that future harms would necessarily have occurred.

The temptation in such situations is to defer further research and development until a national commission or ethics advisory body puts its imprimatur on the practice. While such bodies, however, have been absent from bioethical debate in the United States for some time, there now appears to be an increased willingness to confront such issues. For example, an advisory panel on embryo research has been created to recommend guidelines for federal funding. 14 However, it remains uncertain when any such body will consider the complicated issues of human cloning.

As a result, we are left to elucidate and resolve on a retail basis the ethical dilemmas that each new innovation presents. Cloning by embryo splitting is another example of this policymaking process. Unless there are greater risks from its use than are now apparent, the case for adding the technique to the armamentarium of infertility treatments is a reasonable one. Its novelty will not prevent parents from loving and acting in the best interests of children born in this way.

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IAC-NUMBER: IAC 15244429

IAC-CLASS: Health

LANGUAGE: ENGLISH

LOAD-DATE: September 07, 1995