# Uneven Inheritance

## *A genetic quirk leaves some people with a chromosomal odd couple*

By RICK WEISS

Arthur Beaudet's goal as a molecular biologist seemed straightforward enough: Find the gene causing cystic fibrosis, the most common inherited disorder among U.S. Caucasians. Instead, he stumbled across the first documented case of human uniparental disomy.

This subtle but bizarre genetic phenomenon, still poorly understood by scientists, gives a child double doses of some genes from one parent and no equivalent genes from the other.

Beaudet's odd finding, published in 1988, drew far less attention than the discovery of the cystic fibrosis (CF) gene by other scientists the following year. But a growing body of evidence now has geneticists suspecting that uniparental disomy may be more common than originally thought and may underlie a whole range of inherited disorders.

Indeed, say researchers who are delving into the topic, if uniparental disomy has yet to enter the lay person's lexicon, it's not because the chromosomal quirk occurs so rarely. Rather, the majority of embryos harboring the abnormality probably don't survive to term, as the genetic defect can trigger spontaneous abortion. And those that do survive may go on to show only subtle abnormalities, such as short stature or mild learning disabilities.

Research suggests that some people with uniparental disomy do suffer problems related to the genetic duplication within their cells. But only in the past few years have molecular biologists had the research tools needed to identify these individuals and to explore the mechanisms that led to their strange genetic makeup.

Identifying and studying these people could yield a number of benefits, researchers say. At the very least, it may shed new light on the mechanics of cell division, chromosomal segregation and sexual reproduction. It also may clarify aspects of another mysterious phenomenon, known as genetic imprinting, in which identical genes behave differently depending upon the gender of the contributing parent (SN: 5/20/89, p.312).

Perhaps most intriguing is the possibility that uniparental disomy may cause errors in some prenatal tests for inherited defects. Moreover, the abnormality may provide a genetic rationale for a host of inherited disorders that today have no unifying explanation or apparent molecular basis.

"We'd like to look for uniparental disomy in many of the large number of syndromes we believe are inherited but that don't show evidence of chromosomal deletions," says Judith G. Hall, a geneticist at the University of British Columbia in Vancouver.

Uniparental disomy may provide the genetic loophole that clarifies a host of "impossible" inheritance patterns, she says, by allowing geneticists to dismiss one parent's expected chromosomal contribution. "It's made us look at a variety of syndromes for which we've had no good genetic explanation," Hall says.

Beaudet, a geneticist at Baylor College of Medicine in Houston, was searching for blood when he made his unexpected discovery. His ongoing quest for the CF gene meant that he, like so many other researchers, needed blood specimens from as many people as possible with the disease. By scanning for genetic abnormalities in the DNA of these people's blood cells, Beaudet hoped to identify some inherited defect common to everyone with cystic fibrosis.

"We were interested in cloning the CF gene, so we were looking for gene deletions in some CF patients," Beaudet recalls. "We asked in general clinical meetings—we asked everyone to tell us about cases they had."

Then, at a scientific meeting in Washington, D.C., a physician from upstate New York told Beaudet about a CF patient who was abnormally short. Beaudet arranged to have some of the woman's blood sent to him. Knowing the rule that CF appears only in people who inherit the gene from both parents, he also got blood samples from the woman's father and (because the mother was unavailable for study) from her mother's mother.

"The remarkable thing, when we studied [the patient's] DNA, was that her chromosome 7 was missing any contribution from her father," Beaudet says. In other words, in looking at the two copies of chromosome 7 present in each of the woman's cells—one copy from the mother and the other presumably from the father—the researchers discovered that neither chromosome had a genetic "fingerprint" matching either of the number 7 chromosomes in her father's blood.

"Of course, the first thing we thought was nonpaternity," Beaudet says. But further analysis revealed that the woman

clearly had inherited other genes from her father. Only the chromosome 7 lacked a contribution from her dad.

"Then we thought, 'Aha, a deletion.'" The chromosome 7 provided by the woman's father, Beaudet reckoned, must have been lost during his daughter's early development, leaving her with only a maternal version of chromosome 7.

Wrong again. The woman had inherited two copies, just as she should have.

At last, by comparing both of the woman's number 7 chromosomes, Beaudet found the unexpected solution to the riddle: Her mother had contributed both, while her dad's chromosome 7 had somehow missed the genetic boat. "It took a lot of genetic detective work to confirm that this man was indeed her father and that she simply had two copies of the chromosome from her mother," Beaudet says.

Unfortunately for the woman, her mother carried the CF gene, which resides on chromosome 7.

"Her daughter got two copies of the chromosome, including two copies of the CF gene," Beaudet says. Had she received only one copy from her mother, as usual, and a normal chromosome 7 from her father, she would have escaped the disease. Instead, the woman faced a shortened lifetime of chronic, debilitating lung infections. It was simply a case of genetic bad luck.

In the past decade, geneticists have theorized that some children might inherit an uneven distribution of chromosomes, getting a greater proportion from one parent than from the other. Studies have shown that this occasionally occurs in mice, but until recently scientists had little evidence that it happens in humans.

Some of the first and best hints came from Eric Engel, a geneticist at the University Institute of Medical Genetics in Geneva, Switzerland. His analyses of tissue samples from spontaneously aborted fetuses revealed a surprising number of trisomies (cells containing double contributions from one parent in addition to a normal complement of chromosomes from the other parent) and X-chromosome monosomies (cells containing one, rather than two, sex chromosomes).

Trisomies are not unknown in adult humans, but they are unusual. Down's syndrome, for example, appears in people who inherit three copies of chromosome 21 instead of the usual two. Engel began to suspect that if so many trisomies occur at conception — as evidenced by the large number seen among spontaneously aborted fetuses — then a significant number of surviving individuals might also carry two copies of genes from a single parent.

Engel described these ideas in a paper titled "A New Genetic Concept," published in a 1980 AMERICAN JOURNAL OF MEDICAL GENETICS. In that article he coined the phrase "uniparental disomy" and presented a possible cellular scenario to account for the phenomenon.

The crucial error, he proposed, would occur during meiosis — the process of cell division that creates eggs and sperm, each of which bears half the adult complement of chromosomes. During meiosis, chromosome pairs normally part ways and head toward opposite sides of the dividing cell. Thus, one member of each pair ends up in each progeny cell — be it sperm or egg. Scientists have a lot to learn about the mechanics behind this segregation process, but they do know that chromosomal sorting doesn't always go smoothly.

"Nature is bold and oftentimes plays with fire," Engel comments. "It's lovely that when two people want to have a child we have to divide our chromosomal numbers in half. But this mechanism is risky, because there's always a possibility of

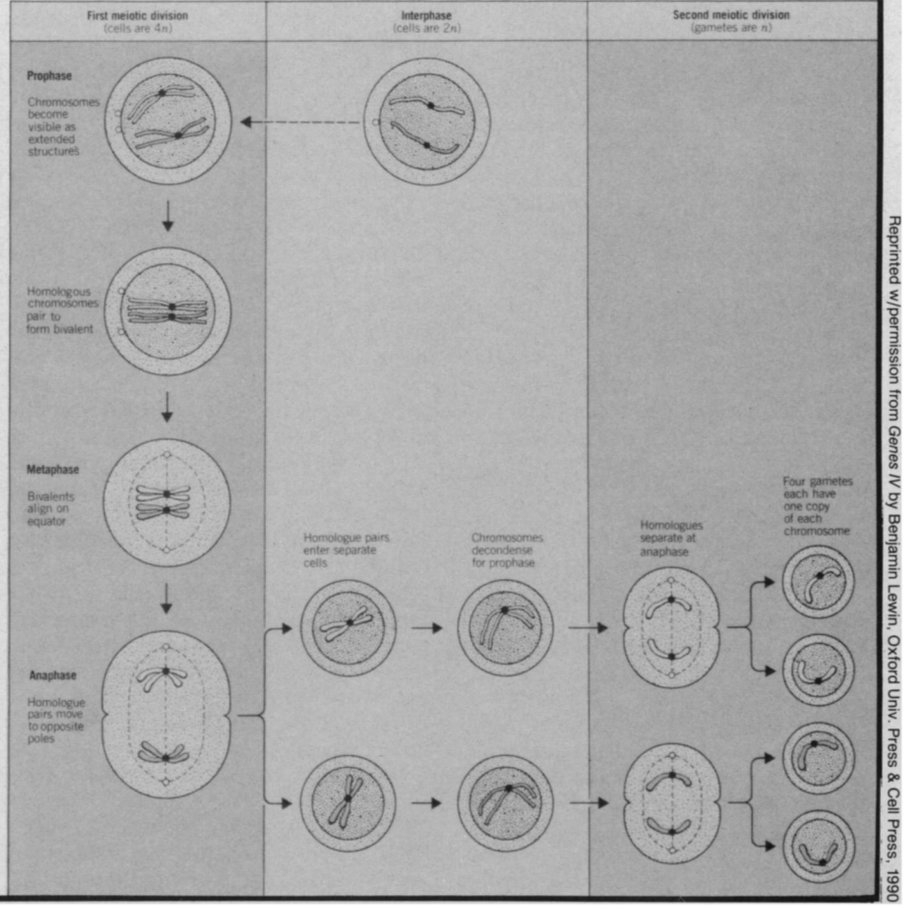
## Meiosis at a glance: The roots of uniparental disomy

Normal sexual reproduction ensures substantial mixing and matching of genetic elements from diverse individuals. But if each parent were to contribute his or her entire genetic inheritance, offspring would accumulate increasingly large amounts of DNA.

Nature avoids this problem through meiosis. The three-step process produces sex cells, each of which contains half the usual number of chromosomes. These cells — the sperm and egg — merge during fertilization to create a new, genetically recombined cell with the normal complement of DNA.

Most human cells contain 23 pairs of chromosomes, with half of each pair contributed by each parent. The first step of meiosis involves a chromosomal doubling to 46 pairs. Following that, two successive cell divisions lead to the creation of four sperm or one egg and three nonfunctioning nuclei, each containing 23 unpaired chromosomes.

Errors in chromosomal segregation during either of these two stages of cell division can lead to the creation of a DNA-heavy sex cell containing twice the normal complement of certain genes. When fertilization takes place between this and a normal sex cell, the result is uniparental disomy, in which a child inherits more than the usual amount of DNA from one parent. — *R. Weiss*



error in the process."

During meiosis, as Engel describes it, chromosomes engage in a carefully choreographed dance. "The members of each [chromosome] pair become intertwined," he says, and individual chromosomes "embrace before separating."

But in some cases, this embrace is too brief and the freed chromosomes start to wander off asymmetrically, "like dogs without a leash," Engel says. "We do not know for sure why this abnormal separation of chromosome pairs occurs. But the process has built into itself many chances of error."

The result is a sperm or egg cell containing two copies of a particular chromosome, or at least two copies of a part of that chromosome. When this cell fuses with another sex cell during fertilization, any of several things may happen.

If a trisomic individual is conceived, and if the trisomy is viable, the child may be born with a disorder such as Down's syndrome. Alternatively, a trisomic embryo may, in a future cell division, lose one copy of the extra genetic material and end up having a normal amount of DNA but lacking one parent's contribution.

In some cases, the trisomy never occurs: DNA from a normal sex cell may never even integrate into a newly fertilized cell that already has two copies of that DNA segment. Again, this could leave an individual with a normal number of chromosomes but lacking one parent's contribution.

Engel recognized that it wouldn't be easy to detect uniparental disomy in living adults. In most cases, a quick look at a person's chromosomes would show nothing more than the usual 23 pairs resting in every cell. Only a detailed analysis with molecular probes capable of revealing the sequence of DNA subunits, or bases, could reveal that both members of a chromosome pair came from the same parent.

When Engel published his 1980 paper, DNA probe technology wasn't quite up to that task. "The proof really came when molecular studies allowed us to look at the sequence of bases that comes from each parent," he says.

It was molecular studies like these, which became commonplace in the late 1980s, that allowed Beaudet to identify the first known case of uniparental disomy in a human – and the first case of human disease for which uniparental disomy could clearly take the blame.

Since Beaudet's discovery, researchers in Israel also have attributed a CF case to uniparental disomy. Extrapolating in part from those two examples, geneticist Hall hypothesizes that as many as one in 500 CF cases may be due to uniparental disomy. "It makes you think, 'Gosh, this is more common than we expected,'" she says. "It makes you wonder how many other childhood disorders may be due to uniparental disomy."

In fact, geneticists have identified at least seven other clear examples in which people inheriting duplicate copies of one parent's genes ended up with a disease that otherwise would have been "cancelled out," and thus prevented, by the presence of the other parent's normal gene.

Last year, a team led by Robert D. Nicholls, Joan H.M. Knoll and Marc Lalande at Children's Hospital in Boston identified six cases of Prader-Willi syndrome attributable to uniparental disomy, which Nicholls described at last October's meeting of the American Society of Human Genetics (SN: 11/18/89, p.324). This rare, inherited syndrome, characterized by obesity, low IQ and a lack of muscle tone, usually results when a segment of the paternally contributed chromosome 15 somehow gets deleted early in development.

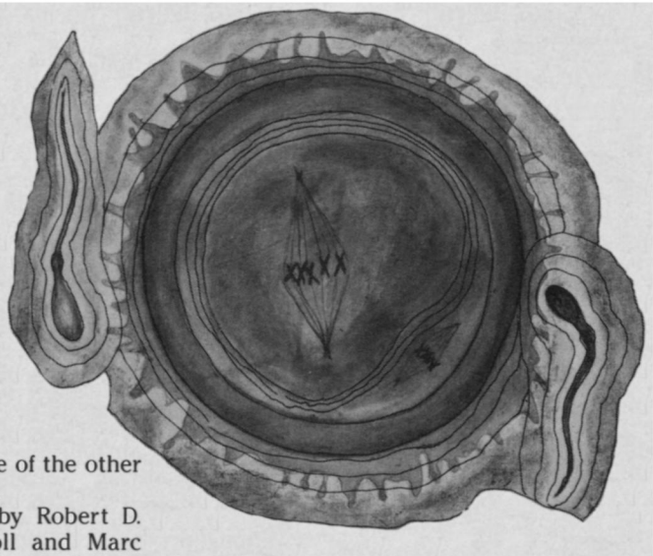
For this reason, most Prader-Willi patients have but a single copy of that chromosomal segment – the copy contributed by the mother. Oddly, all six patients in the Boston study had two copies of the chromosome 15 segment – but with both copies contributed by their mothers.

"It throws us off in the immediate way we look for some genetic abnormalities," says Nicholls, now at the University of Florida College of Medicine in Gainesville.

Normally, he explains, geneticists use DNA probes – bits of genetic material that help find particular stretches of DNA in a person's cells – to look for DNA deletions that can cause disease. In cases of uniparental disomy, however, no such deletions exist. Or, seen another way, whatever deletion has occurred is "filled in" with a duplicate stretch of DNA from the one contributing parent.

Disomy is still detectable, Nicholls says, "as long as you're aware it may be there and you have the proper probes." But most genetic tests today don't look for duplications, which are harder to detect than deletions or blatant errors in the number of chromosomes. Thus, standard tests for certain inherited diseases – including some prenatal tests for diseases such as Prader-Willi syndrome – will miss those cases involving uniparental disomy, he says.

French researchers at the October meeting presented another example of disease attributable to uniparental disomy. It involved a boy with




hemophilia A, an inherited bleeding disorder caused by a defective gene on the X chromosome.

Men have one X chromosome and one male-determining Y chromosome, while women have two X chromosomes. Each parent contributes only one of his or her sex chromosomes to the child. Thus, newborn males (XY) always inherit their Y chromosome from the father. Their X chromosome – sometimes bearing a hemophilia gene – can only come from the mother.

D. Vidaud and his colleagues became suspicious when they found a hemophiliac boy whose mother had no family history of the disease. His father's family did have a history of hemophilia, but since fathers normally contribute only a Y chromosome to their sons, it would seem impossible for the boy to have inherited this X-linked disease from his dad.

After extensive analysis of seven of the boy's chromosomes and those of his parents – in part to confirm parentage – the French researchers determined that the boy had inherited both his X and Y chromosomes from his father and had received no sex chromosome from his mother.

In theory, because his mother's X chromosomes carried no hemophilia genes, the boy had no chance of being born a hemophiliac. Uniparental disomy changed those odds.

How often does uniparental disomy really occur? An editorial accompanying Beaudet's CF case report in the February 1988 AMERICAN JOURNAL OF HUMAN GENETICS predicted the phenomenon would prove "exceedingly rare." However, Beaudet now says, "I'm unwilling to accept that this is all that rare."

Nicholls agrees. "At first, we thought it would be a very rare event. We're now finding that it's not so rare."

So far, most of the evidence for the phenomenon's frequency is indirect. Hall notes that cell biologists find evidence of

trisomy in 2 to 5 percent of tissue samples taken from fetuses during prenatal testing. "That's pretty high," she says. She suggests that most of those surviving to birth somehow lose their extra chromosome during development. If the disappearing chromosome originally came from the parent who contributed only one, then the child may harbor cells that are uniparentally disomic.

Along similar lines, Engel notes that about half of all fetuses spontaneously aborted during the first trimester show chromosomal abnormalities, and that many of these defects result from errors during meiosis. This, along with evidence from mice, suggests to him that the chance of a person ending up with uniparental genetic duplication is higher than many scientists suspect.

"Maybe sometimes it doesn't carry any bad effect with it," Engel says. Unless the disomy encompasses a mutant gene that requires a duplicate presence to cause disease, as in the case of CF, "you may have perfectly normal people with no problem," he suggests.

Well, *almost* no problem. Many geneticists suspect that even when no particular disease gene gets involved, uniparental disomy can have subtle effects. These influences have their roots in the phenomenon of genetic imprinting.

Geneticists have found that certain otherwise identical genes show differences depending upon which parent – male or female – contributed the genes. In biologists' jargon, the gene from one parent gets "imprinted" with a molecular marker indicating whether it has come from the mother or father. In these cases, it's critical that a child receive both imprinted and nonimprinted versions of that gene for proper development; two paternal versions or a pair of maternal ones simply won't do.

So in some cases, uniparental disomy may leave a fetus viable but with subtle abnormalities resulting from the lack of mixed maternal and paternal genes. Hall and others suggest, primarily on the basis of mouse studies, that human uniparental disomy involving chromosomes that normally bear imprinted genes can result in mild developmental problems, including short stature and learning disabilities.

Indeed, these geneticists suspect that the short stature of Beaudet's CF patient stemmed from her lack of certain imprinted genes. Geneticists already know that certain genes on paternal copies of chromosome 7 are normally imprinted in mice, and without that paternal complement of imprinted genes, development proceeds abnormally.

Every time nonimprinted DNA substitutes for imprinted DNA, "you'd expect to get someone with short stature," Beaudet says. "And if [the nonimprinted DNA] includes the CF gene, then you'd have cystic fibrosis too."

That kind of thinking has spurred Hall and her colleagues to begin looking for hidden cases of uniparental disomy among healthy, short-statured people – especially those showing subtle behavioral problems like those seen in mice with imprinting abnormalities. "We're looking for kids with abnormal growth patterns and [abnormal] behavior," she says. "We've started looking at some of these individuals and testing them for uniparental disomy."

In addition, Hall, Engel and others expect that as geneticists analyze DNA from people with inherited disorders of unknown cause, they will begin to find uniparental disomy at the roots.

"There's a sense that [uniparental disomy] might be more common than has been thought, and that the mechanism may explain a few or a number of syndromes that thus far have no explanation," Engel says. "As in Prader-Willi, there are some syndromes where there usually is a tiny chromosomal deletion, and some of the cases don't show such a deletion. One might envision that disomy might explain these rare syndromes."

Among the unexplained, inherited abnormalities that Engel mentions as candidates are Beckwith-Wiedemann syndrome, Miller-Dieker syndrome and Silver-Russell syndrome. Each involves variations of growth retardation and congenital anomalies.

But in order to peg these or other syndromes to uniparental disomy, researchers need to perform detailed analyses of the DNA base sequence on all 23 pairs of human chromosomes, studying both the person in question and his or her parents. And although the number of DNA probes grows every month, the current selection still leaves large chromosomal regions essentially unmappable.

Ultimately, as more and more human chromosomes bare their secrets to genetic probes, prenatal testing may routinely include searches for uniparental disomies. In coming years, Engel predicts, "molecular probes will detect these and tell us more about their frequency."

While Engel looks forward to learning those details, he says he also hopes researchers and parents will not become obsessed with genetic analyses of every developing fetus. "To tell the truth," he says, "I think that would take all the beauty out of human procreation." □

*News of the week continued from p.7*

# Shuttles grounded by two sets of leaks

It proved a double blow to proud NASA. As astronomers pondered the consequences of an apparently misshapen mirror that significantly reduced the Hubble Space Telescope's ability to explore the distant heavens, engineers at Kennedy Space Center in Florida discovered yet another hydrogen leak in a space shuttle. A month ago, the space agency delayed the flight of Columbia because of such a leak. This time, Atlantis revealed a similar and possibly related leak.

NASA, which had already postponed Columbia's mission until at least August, reacted to this second potentially lethal problem by indefinitely suspending flights by the three shuttle craft. William B. Lenoir, NASA's chief of space flight, said the shuttles would remain grounded until engineers found, understood and fixed the leaks.

No one ventured a specific date when the shuttle fleet might fly again.

Liquid hydrogen and liquid oxygen serve as the propellants for the shuttle orbiter's three powerful main engines that help drive the craft into space. The two supercold fluids fill the huge external fuel tank that clings to the underside of the astronaut-carrying orbiter and flow through a complex system of pipes and valves to the main engines. The fuel mixture is highly explosive.

Hydrogen has no scent or color, and spotting hydrogen leaks requires special detectors. It is far more difficult to locate a leak and repair it than to simply confirm that one exists. Engineers have been conducting tests of each craft's external tank and its piping, as well as of the "umbilical" connecting hoses and the fittings used to fill the tanks.

The leak studies now focus on four themes, Lenoir says. One involves a detailed analysis of how the pieces that make up the propellant-storage and delivery components were made. A second concentrates on how this equipment was handled, assembled and shipped. A third line of investigation is devoted to step-by-step data analysis of the system, checking to make sure engineers haven't overlooked some possible leak source. And the fourth, reminiscent of the Challenger investigation, creates and follows "fault trees" designed to anticipate subtle flaws – in design, fabrication or other aspects – that might trigger equally disastrous consequences.

Columbia had been scheduled for a May launch to carry Astro-1, a four-telescope observatory that will study the sky from the shuttle's cargo bay rather than from a "free-flying" satellite like the Hubble Space Telescope. Atlantis had been scheduled to deploy a classified satellite for the Department of Defense.

*– J. Eberhart*