Letter From the Desk of David Challinor
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"Male and female he created them," Genesis records. Being male or female is essential for those organisms that reproduce sexually, as opposed to parthenogenetically (self-fertilization) by the female; in the latter case all progeny are female, such as in some populations of Caucasian rock lizards (*Lacerta saxicola*). Bacteria and many plants reproduce themselves in yet another fashion: they merely split and clone themselves. There are advantages and disadvantages to the various methods of reproduction, but clearly, if the species exists, the pluses must outweigh the minuses. This month's letter will discuss male and female mammals—particularly humans—and how certain relatively small gender differences enable us to perpetuate our species. It will include a great deal of information about which I was unaware of until a few years ago. I am delighted to report that no matter what the age, if one stays alert something new can be learned daily.

The sexual differences between men and women are relatively trivial when we consider the magnitude of shared characteristics. Both sexes must eat, sleep and communicate; we show the same emotions—generally, we laugh at the same jokes or are saddened by the same events. This is not surprising when we consider that all of us started out as ambiguously female. Let me explain.

When the egg from which we began was extruded from our mother's ovarian follicle, it started its voyage down a hair-thin tube (fallopian). There it met the small group (compared to the number that began the trip) of male gametes (sperm cells) that had survived the perilous journey through a hostile environment. Of the roughly 180 to 200 million initial male cells, most succumbed to the strong acid environment through which they had to pass. The cervix was another considerable barrier, and the few thousand sperm that successfully reached the tube represented in many respects Darwin's "survival of the fittest."

The single successful male gamete that attaches to the ovum triggers one of the fastest immune reactions in nature: once connected, all other male cells are rejected. The fertilized ovum then becomes a blastocyst. This body of busily dividing cells drops into an elegant nursery (the uterus), where it floats around for 12 to 14 days before implanting on the endometrium (the lining of the uterus). Prior to implantation, this collection of cells is indistinguishable between the sexes. Implantation is the magic time for humans for two reasons: first, the reader and I are the lucky ones, because only slightly more than half (about 55-60%) of our mother's blastocysts successfully implant. Second, this is when the dividing cells start the process of sex determination. For the first six weeks *in utero*, the embryo is double-sexed—that is, it is developing gonads that could become the reproductive organs of either a male or a female. If the embryo has inherited an X-chromosome (a big one with 1500 genes) from the father (we all have an X from our mother), the embryo develops into a girl. However, if it has a Y-chromosome (a small one with only about 78 genes) one of those genes called *Sry* asserts itself and signals the dividing cells to produce a male. In other words, it takes a positive action by this one small gene to produce a boy. The rest of the genes on the Y-chromosome are evidently not crucial to survival, as females do fine without them.

This short summary of the miraculous process through which each of us passed becomes even more incredible as we grow *in utero* and then, through a remarkable series of exquisitely timed hormone releases, develop properly and are born.

A female with two X-chromosomes must have a mechanism to decide, as she grows *in utero*, which X-chromosome will furnish the genes for her multiplying cells. For example, the gene for seeing colors is on the X-chromosome. If one parent is colorblind, which X gene—her father's or her mother's—will the female embryo receive? What happens to the unused X? We are now beginning to understand the consequences of being XX instead of XY. Virtually every female is, therefore, a combination of two different X-chromosomes; this makes them considerably more genetically complicated than men because the X-chromosome carries so many more genes than the Y-chromosome. The human Y-chromosome has only recently been decoded and scientists are just now learning what some of the other Y genes control.

When the X-chromosome was discovered, it was quickly recognized as being unique because it is the only full-sized chromosome that healthy humans, whether male or female, can have singly or doubly. Normally chromosomes are paired—one from each parent—but the X-chromosome is an extraordinarily powerful one of which men have only an unpaired one. If the X is this potent, why are women overloaded with two X's?

The answer was discovered in 1960 when Mary Lyon, a British geneticist, put two seemingly unrelated facts together. The first was that cells in female mammals contain a small object called a Barr body not found in male cells. The second was that females of certain cat strains can have mottled coat colors while males never do. Lyon's theory was that females somehow switched off one of the two X's in every cell of her body and "tied up" the unused X in a little package called a Barr body (a small speck in the nucleus of each of her cells). She went on to propose that very early on—as an embryo—each of the female cat's cells inactivates an X randomly and that eventually, the cells with an inactivated X form patches or collections of cells that keep all these X-chromosomes in an inactive condition. What this means is that females consist of a mixture of two different cell types. Because the X-chromosome carries about 5% of our total genetic makeup, the two separate halves of a woman can be quite different genetically. Monozygotic (identical) twin girls are remarkably less identical then identical twin boys, because when a female embryo divides to form twins, each inherits very similar genes. Yet the process can affect them differently because X-inactivation is random in the two embryos. In extreme cases, one female twin can suffer from a genetic disease and the other be free of it. The afflicted one received a damaged gene on her X-chromosome, whereas the healthy one used the equivalent undamaged gene on her other X-chromosome. Fortunately, these mismatches are rare and seemingly are not randomly triggered. If such mismatches are not at random, then one theory is that the process of X-inactivation may be the cause of twinning—that the two X's under certain conditions might repel each other causing the embryo to split in two. One piece of evidence to support this theory is that twinning and X-inactivation occur at about the same time when the embryo is implanting. There remains a great deal more research to be done to account for this dual genetic nature of females.

The foregoing discussion about the role of X- and Y-chromosomes in mammalian reproduction indicates that there are still many gaps in our understanding. This begs the question: Why have sexual reproduction at all? We know that Caucasian rock lizards can reproduce without males. Those who have read Aldous Huxley's Brave New World will recall his futuristic culture where externally fertilized ova produce blastocysts that are "budded" to create 72 to 96 identical "embryos," which are then matured on artificially maintained endometria. This is obvious fiction and a quite unlikely scenario. Although I believe that mammal ova have been triggered to divide synthetically, continued division did not occur until the recent cloning experiments. However, more than 30 years ago at the Department of Agriculture's Research Station in Beltsville, MD scientists experimentally produced a small flock of haploid (one W-chromosome) turkeys. Birds do not have X and Y, but rather males have one Z and females two W's. All progeny were female, infertile, seemingly identical and slightly smaller than a normal hen turkey. Once completed, I do not believe the experiment was ever repeated there.

One advantage of sexual reproduction is that genes are mixed. The variation among individuals helps ensure that the best-adapted will survive under changing physical conditions. Genetic variation may also be an effective way to confuse parasites, as suggested by the late W.D. Hamilton of Oxford University. Clearly for humans, sexual reproduction has been successful, perhaps too successful according to those concerned about unbridled population growth in some parts of the world. People have been fascinated with behavioral differences between men and women, but I wonder how much generalization is justified and are these differences really important? There are no psychological characteristics in which all men are different from all women and visa versa. We must, therefore, judge each other on the basis of individual characteristics and not on gender. Although this seems to be a reasonable conclusion, many prejudices are perpetuated in such books as Men are from Mars, Women are from Venus. I do not advocate androgyny, but I honestly believe men and women in this country during my lifetime have indeed learned a greater degree of mutual respect. An extraterrestrial observer might comment: “It’s about time.”

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P.S. Much of the information in this letter came from a recently published fascinating book: The X in Sex, How the X-Chromosome Controls our Lives, by David Bainbridge, Harvard University Press, Cambridge, MA. 2003