

Human Chimeras

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A chimera is an ordinary person or animal except that some of their parts actually came from their twin or from the mother. A chimera may arise either from monozygotic twin fetuses (where it would be impossible to detect), or from dizygotic fetuses, which can be identified by chromosomal comparisons from various parts of the body. The number of cells derived from each fetus can vary from one part of the body to another, and often leads to characteristic mosaicism skin colouration in human chimeras. A chimera may be a hermaphrodite, composed of cells from a male twin and a female twin.

Chimera: In medicine, a person composed of two genetically distinct types of cells. Human chimeras were first discovered with the advent of blood typing when it was found that some people had more than one blood type. Most of them proved to be “blood chimeras” — non-identical twins who shared a blood supply in the uterus. Those who were not twins are thought to have blood cells from a twin that died early in gestation. Twin embryos often share a blood supply in the placenta, allowing blood stem cells to pass from one and settle in the bone marrow of the other. About 8% of non-identical twin pairs are chimeras.

Many more people are microchimeras and carry smaller numbers of foreign blood cells that may have passed from mother across the placenta, or persist from a blood transfusion. In vitro fertilization (IVF) is also contributing to the number of human chimeras. To improve success rates, two or more embryos are placed in the uterus so women who have IVF have more twin pregnancies than usual. More twins mean more chimeras.

Chimera mythology :

In Greek mythology, the Chimera was an awesome fire-breathing monster with the head of a lion, the body of a goat, and the tail of a serpent. The Chimera was killed by the hero Bellerophon mounted, in most versions of the tale, on Pegasus, the winged horse. The Chimera (Greek $\times\beta\acute{\iota}\acute{\alpha}\acute{\epsilon}\acute{\nu}\acute{\alpha}$ (Chímaira); Latin *Chimaera*) was a

monstrous creature of in Asia Minor, composed of the parts of multiple animals. The Chimera was one of the offspring of Typhon and Echidna and a sibling of such monsters as Cerberus and the Lernaean Hydra.

Tetragametic chimerism:

Tetragametic chimerism is a less common cause of congenital chimerism. It occurs through the fertilization of two ova by two sperm, followed by the fusion of the zygotes and the development of an organism with intermingled cell lines. This happens at a very early stage of development, such as that of the blastocyst. Such an organism is called a tetragametic chimera as it is formed from four gametes — two eggs and two sperm. Put another way, the chimera is formed from the merger of two nonidentical twins in a very early (zygote or blastocyst) phase. As such, they can be male, female, or hermaphroditic.

As the organism develops, the resulting chimera can come to possess organs that have different sets of chromosomes. For example, the chimera may have a liver composed of cells with one set of chromosomes and have a kidney composed of cells with a second set of chromosomes. This has occurred in humans, and at one time was thought to be extremely rare, though more recent evidence suggests that it is not as rare as previously believed. Most will go through life without realizing they are chimeras. The difference in phenotypes may be subtle (*e.g.*, having a hitchhiker’s thumb and a straight thumb, eyes of slightly different colors, differential hair growth on opposite sides of the body, etc) or completely undetectable. Another tell tale of a person being a chimera is visible Blaschko’s lines.

Affected persons are identified by the finding of two populations of red cells or, if the zygotes are of opposite sex, ambiguous genitalia and hermaphroditism alone or in combination; such persons sometimes also have patchy skin, hair, or eye pigmentation (heterochromia). If the blastocysts are of the same sex, it can only be detected

through DNA testing, although this is a rare procedure. If the blastocysts are of opposite sex, genitals of both sexes are often formed, either ovary and testis, or combined ovotestes, in one rare form of intersexuality, a condition previously known as *true hermaphroditism*. As of 2003, there were about 30-40 documented human cases in the literature, according to *New Scientist*. Since hermaphroditic chimeras would be expected to be half of all chimeras, with purely male and purely female chimeras being one-quarter each, this would suggest that the condition is not particularly common.

Natural chimeras are almost never detected unless the offspring has abnormalities such as male/female or hermaphrodite characteristics or skin discolouring. The most noticeable are some male tortoiseshell cats or animals with ambiguous sex organs. Recent studies of tortoiseshell male cats and unusually coloured tortoiseshell-like cats suggest that natural chimerism is far more common than previously realised and that it frequently goes undetected.

Chimerism can be detected in DNA testing. The Lydia Fairchild case, for example, was brought to court after DNA testing showed that her children could not be hers, since DNA did not match. The charge against her was dismissed when it became clear that Lydia was a chimera, with the matching DNA being found in her cervical tissue. Another case was that of Karen Keegan.

The tetragametic state has important implications for organ or stem-cell transplantation. Chimeras typically have immunologic tolerance to both cell lines. Thus, for a tetragametic human, a wider array of relatives and other persons may be eligible to be an organ donor.

Microchimerism:

Microchimerism is the presence of a small number of cells, genetically distinct from those of the host individual. The most common form is fetomaternal microchimerism (or fetal chimerism) whereby cells from a fetus pass through into the mother. Fetal cells have been documented to persist in maternal circulation for as long as 38 years. Microchimerism had also been shown to exist after blood transfusions to a severely immunocompromised population of patients who suffered trauma.

Microchimerism has been implicated in autoimmune diseases. Two independent scientists (Carol M. Artlett and J. Lee Nelson) published data within a month of each other, suggesting that microchimeric cells of fetal origin may be involved in the pathogenesis of systemic sclerosis. Artlett went on to demonstrate that microchimeric cells of maternal origin may be involved in the pathogenesis of a group of autoimmune diseases found in children, juvenile

idiopathic inflammatory myopathies (one example would be juvenile dermatomyositis). Microchimerism has now been further implicated in other autoimmune diseases, including systemic lupus erythematosus. A recent alternative hypothesis of the role of microchimeric cells in lesions is that they may be facilitating tissue repair of the damaged organ. However, although these foreign cells are found in the lesions of autoimmune diseases, their role in the cause of disease is yet to be fully uncovered. Microchimeric cells may be mediating damage, facilitating tissue repair, or simply be innocent bystanders.

Germline chimerism:

Germline chimerism is when the sperm and egg cells of an organism are not genetically identical to its own. It has recently been discovered that marmosets can carry the reproductive cells of their twin siblings, because of placental fusion during development.

Chimeras in research:

In biological research, chimeras are artificially produced by physically mixing cells from two different organisms. Chimeras are not hybrids, which form from the fusion of gametes from two species (like a donkey and a horse) that form a single zygote that will develop as much as it can (in this case into a live mule if the parents are jackass and mare, or a hinny if the parents are stallion and jenny); in comparison, chimeras are the physical mixing of cells from two independent zygotes: for example, one from the donkey and one from the horse. "Chimera" is a broad term and is often applied to many different types of mixing of cells from two different species.

Some chimeras can result in the eventual development of an adult animal composed of cells from both donors, which may be of different species — for example, in 1984 a chimeric geep was produced by combining embryos from a goat and a sheep. The "geep" has been a very important contributor to answering fundamental questions about development, and the techniques used to create it may one day help save endangered species. For example, if one tried to let a goat embryo gestate in a sheep the sheep's immune system would reject the developing goat embryo; however, if one used a geep that shared markers of immunity with both sheep and goats, the goat embryo may survive. It may be possible to extend this practice for the purpose of preventing the extinction of some endangered animal species.

Such interspecies chimeras such as the "geep" are made in the laboratory and rarely with the purpose of

generating living hybrid animals. In addition to the famous geep, there are rat/mouse chimeras and a rabbit/human chimera which was destroyed within a few days for the purpose of harvesting stem cells. Intraspecies chimeras are created by transplanting embryonic cells from an animal with one trait into an embryo of an animal with a different trait. This practice is common in the field of embryology and has been a very important contributor to our current understanding of human and animal biology. For example, by mixing embryonic cells of differently coloured or otherwise genetically distinct mice (of the same species), researchers have been able to see how embryos form and which organs and tissues are related (arise from the similar cell lineages).

Hybridomas are not true chimeras as described above because they do not result from the mixture of two cell types but result from fusion of two species' cells into a single cell and artificial propagation of this cell in the laboratory. Hybridomas have been very important tools in biomedical research for decades.

In August 2003, researchers at the Shanghai Second Medical University in China reported that they had successfully fused human skin cells and dead rabbit eggs to create the first human chimeric embryos. The embryos were allowed to develop for several days in a laboratory setting, then destroyed to harvest the resulting stem cells. Because of the high therapeutic potential of human embryonic stem cells and the United States moratorium on using discarded embryos from in vitro fertilization clinics as well as other concerns about using human embryos

directly for research, scientists are trying to find ways to find alternative paths of research. However, increasingly realizable projects using part-human, part-animal chimeras as living factories not only for biopharmaceutical production but also for producing cells or organs (see hybridomas) for xenotransplantation raise a host of ethical and safety issues.

During November 2006, UK researchers from Newcastle University and King's College London applied to the Human Fertilisation and Embryology Authority for a three-year license to fuse human DNA with cow eggs. The proposal is to insert human DNA into a cow's egg which has had its genetic material removed and then create an embryo by the same technique that produced Dolly the Sheep. The resulting embryo would be 99.9% human; the only bovine element would be DNA outside the nucleus of the cell. This research was attempted in the United States several years before and failed to yield such an embryo. In April 2008 the researchers from Newcastle University reported that their research had been successful. The resulting embryos lived for 3 days and the largest grew to a size of 32 cells. The researchers are aiming for embryos that live for 6 days so that embryonic stem cells can be harvested.

In 2007, scientists at the University of Nevada School of Medicine created a sheep that has 15% human cells and 85% animal cells.

