for grants, writing papers, performing administrative tasks, reviewing papers and, if time permits, doing research themselves. This is inefficient because it is difficult to ensure long-term continuity of research expertise in labs as trainees complete their training and move on. Worse still, there is scarcity of permanent (or renewable), non-training research positions available for the numbers of trainees trained. Many trainees do not want to become a professor or work in government or industry; they want to continue to do academic research. Permanent, or indefinitely renewable, postdoctoral research associate positions would allow the retention of such talented scientists, ensure the continuity of expertise in a research group and help with the training of new students. However, such positions are costly and require long-term, stable funding for academic research groups from either universities or granting agencies; that is rare in most countries.

Do you see any problems with how science is done these days? One concerning trend is the growing confusion between respectful, scientific debate and personal criticism. Vigorous disagreement and argumentation about scientific points is absolutely critical to expose flaws in interpretations, hypotheses or accepted 'facts'. As Karl Popper famously put it, "the growth of knowledge depends entirely upon disagreement." On the other hand, conflict of a personal nature usually becomes a battle between egos that stifles scientific discourse. The problem comes when scientists are afraid to raise points of legitimate criticism for fear of causing personal offense and inviting retribution. Furthermore, it seems few journals these days want to publish critiques of papers that they have published. As a result, questionable claims in the literature can go unchallenged and become orthodoxy.

But how do you avoid personally offending scientists whose claims you are criticizing? It is sometimes hard to avoid, but there are ways to criticize respectfully. Focus on the points you wish to criticize (not the person who made them), appeal only to reason and published evidence, and avoid sarcastic or personalized commentary. Try to convince your peers of the validity of your points rather than attempting to 'defeat an opponent'. The flip side is that we all should be prepared to face criticism and accept its necessary role in science. Defend your work and ideas using the same principles of respectful discourse. It is not about whether *you are right*, it is about *what is true*. After the dust settles, if you are wrong, then accept it gracefully.

What do you hope your trainees learn from you? Firstly, good scholarship, scientific rigor, and sound reasoning are more important than hype or short-term fame. Hold yourself to the highest standards, be your own toughest critic and avoid shortcuts. Openly communicate with colleagues and collaborators and share your knowledge. In turn, learn from them, value their wisdom, time and effort and give them appropriate credit. Don't be afraid to admit your ignorance. Stay open to feedback and seek constructive criticism because this is how you grow as a scientist. Embrace new perspectives, methods and technologies if they are truly useful. Finally, it's OK to be wrong and to admit it. The truth is more important than your ego.

Do you always follow these recommendations? No! Unfortunately, I often fail to follow them. But I do *try*!

Any other advice for junior scientists? Two things. First, remember that a career in science is built over the long term; it is a marathon rather than a sprint. Pace yourself and take care of your mental health. Take holidays and make sure to include leisure and recreation in your life because scientific creativity *requires* a rested mind. Second, accept that failure is part of the process of striving for something worthwhile. Experiments often won't work, manuscripts and grant applications will get rejected, and your favorite idea might turn out to be wrong. To be really successful, learn from failure: reflect on what went wrong, embrace constructive criticism and keep trying!

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Quick guide

Sex reversal

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What is sex reversal? Sex reversal is a redirection of sexual phenotype during embryonic development. Most aspects of sexual phenotype, including sex ducts and genitalia, depend on the presence of steroid hormones produced by the testis or ovary. The testis or ovary fate of the gonad is decided through a process called sex determination. During sex determination, the testis and ovary pathways are mutually antagonistic and compete for control of gonad fate. Sex reversal occurs when the sexual trajectory of the gonad is changed to the opposing pathway, switching the sexual phenotype of the organism to the opposite sex.

In mammals and other vertebrates, where sex is primarily determined by a XX/XY or ZZ/ZW genetic chromosomal system (i.e. genetic sex determination), 'sex reversal' refers to the differentiation of a gonadal or sexual phenotype that does not align with genetic sex — for example, the formation of an ovary and female phenotype in an XY animal. In species in which sex determination is influenced by the environment (environmental sex determination), sex reversal also refers to a switch in the sexual trajectory of the gonad to the opposing pathway — for example, the formation of a testis and male phenotype under conditions (e.g. temperature) that normally produce females. With the exception of fish and birds, functional sex reversal — defined as the ability to produce gametes (sperm or egg) of the opposite sex — can only occur during the early stages of gonad development.

How does sex reversal happen? In all vertebrates, the gonads arise as bipotential primordia composed of progenitor cells that can differentiate into cells of either the testis or the ovary. It is this plasticity that makes gonadal sex determination amenable to reversal events, where the fate of the gonad may be

switched during sex differentiation, or even as a mature reproductive tissue in fish. We can think of sex determination happening in three distinct phases: an initiation phase (when the molecular pathway triggering differentiation of the ovary or the testis is activated), a maintenance phase (whereby the ovary or testis pathway is perpetuated and reinforced while the opposite pathway is repressed), and a later, stabilization phase (when the ovaries or testes become functional) (Figure 1). During the initiation and maintenance phases, the gonad is still plastic and sexual fate can be switched to the opposing pathway. Sex reversal often occurs because of a failure to maintain the initiated pathway or a failure to repress the opposite pathway.

In mammals, the sex-determining region of the Y chromosome, *Sry*, initiates the development of the testis from the bipotential gonad. Expression of *Sry* leads to activation of downstream targets in the testis pathway, such as *Sox9*. These targets repress the ovarian pathway, whilst simultaneously activating and maintaining testis differentiation. Sex determination operates like a sensitive balance where any dominating factor may throw the balance in favor of one outcome over the other. Mutations that alter the expression levels of crucial, early testis-determining genes, like *Sry* or *Sox9,* interfere with their ability to activate the testis pathway and repress the ovarian pathway, and can lead to sex reversal, i.e. the development of an ovary and a female sexual phenotype in an XY individual. Sex reversal can also go the other way: when Wnt4, which activates other female pathway genes and represses *Sox9*, is mis-regulated or missing, the male pathway can dominate and lead to the development of a testis and a male phenotype in an XX individual (even in the absence of the *Sry* gene).

As previously mentioned, sex can also be determined through environmental cues, such as temperature. For many reptiles, egg incubation temperature provides a dominant sex-determining cue. In these species, the plastic period of gonad development is longer than in mammals, lasting between 10 and 20 days. A switch in temperature, or exposure of the gonad to hormones, can reverse the sexual trajectory at any time during this period, leading to functional sex reversal in adult life (with the efficiency of reversal decreasing as the end of the maintenance window is reached).

Why is sex reversal functional in some species and not others? At least in mice, sex-reversed XX males cannot produce sperm because genes on the Y chromosome are required for spermatogenesis. But when sex reversal occurs during the initial stages of sex determination, XY females can produce oocytes, although usually only for a very short period. The emergence of morphological differences between a testis and an ovary, and coincident commitment of germ cells to sperm or oocyte development, begins about 3 days after expression of *Sry* is initiated and marks the end of the plastic period in mice. Although loss of critical testis differentiation genes later in fetal development or in adult life causes degeneration of the testis, loss of the male hormone environment, and sometimes trans-differentiation of some cells to ovary fate, this does not result in functional sex reversal to female. Similarly, loss of the critical female gene *Foxl2* or depletion of all oocytes in the maturing ovary leads to degeneration of the ovary, expression of some male genes, and higher testosterone levels in females, but it does not lead to functional sex reversal to male.

In general, species that exhibit environmental sex determination have less-differentiated sex chromosomes or a weak multigenic system that is easily dominated by other influences. The absence of highly differentiated sex chromosomes that contain genes that favor differentiation of one gamete type over another eliminates a major barrier to functional sex reversal.

Is sex change the same thing? No. Unlike sex reversal, sex change is not due to a shift in the balance of the opposing ovary and testis pathways during early gonad development. Sex change happens in the stabilization phase due to activation of an extrinsic pathway for change. Many reef fish can change sex during their adult lives. These fish are sequential hermaphrodites, meaning that, as adults, they transition from one mature sex to the other through a process of degeneration and regeneration of their testes or ovaries. Depending on the species, sex change can be size dependent and/or socially mediated. In clownfish,

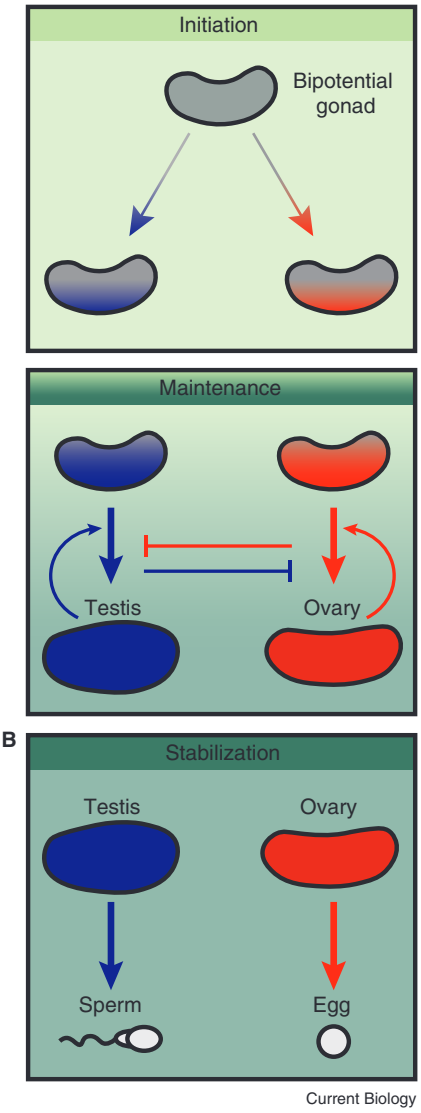

Figure 1. Phases of gonadal sex determination.
Gonadal sex determination happens through distinct phases: (A) initiation and maintenance, and (B) stabilization. Sex reversal can only occur during the initiation and maintence phases, whereas sex change can occur during stabilization.

a dominant female and dominant male make up a breeding pair while all juvenile fish are male. Loss of the dominant female fish triggers the most dominant male to transition into a female. A juvenile male then takes the place of the former dominant male in the breeding pair.

Chickens can also undergo sex change, although they use a different mechanism and can only change from female to male. In birds that are chromosomally female (ZW), only one of the two gonads develops into an ovary in fetal life. If the ovary is damaged, the spare gonad differentiates into a testis that produces androgens and leads to complete masculinization of the bird's phenotype and reproductive behavior. Both fish and chickens can undergo functional sex change, meaning they can transition to produce gametes of the opposite sex.

Partial phenotypic sex change can be initiated after birth in many mammals, and is often related to changes in hormone synthesis or receptivity. The female European mole is an example of a mammal that naturally undergoes seasonal morphological changes in the gonad. The oocyte-producing region of the ovary contracts while the medulla of the ovary expands and produces testosterone, leading to very aggressive behavior during the winter months. However, this does not result in sperm production, and the process is reversed in the spring, when the ovary returns to producing oocytes, and females become receptive to males.

Does the brain change when vertebrates switch sex? Probably. Sex hormones are known to affect brain development, but how completely brain identity is changed may vary among species and may also depend on when the switch occurs. In fish, sex change is closely integrated with visual cues and adrenal hormones that regulate aggressive/submissive behaviors, which are used as readouts for 'brain sex'. It seems likely that the sex change transition is highly coordinated in fish.

When sex is reversed during early gonad development in mammalian models, behavior patterns generally follow suit. For example, expression of *Sry* in an XX embryo leads to sex reversal to male, development of a testis, and production of male hormones that promote male reproductive and aggressive behavior patterns. However, sex chromosome constitution (XX or XY) does affect some aspects of brain development and behavior, which could in theory lead to a mismatch of sexual behavior or identity with primary sex characteristics controlled by gonadal hormones.

This is a difficult question to study because sexually dimorphic reproductive behaviors are typically used as a readout for 'brain sex' in animal models, but we know from humans that sexual behavior is not a very accurate measure of sexual identity. Although there has been considerable, cross-disciplinary research on the relationship between physiological sex, gender identity, and sexual behavior, we are still a long way from understanding how prenatal hormones, gonadal sex, postnatal hormones, sex chromosome constitution, and socialization affect our sexual identity and behavior patterns.

Is sex reversal adaptive?
Sometimes. The transition from one sex to another is an advantageous reproductive strategy in animals such as reef fish. It's been hypothesized that this improves fish survival and enhances reproduction by maintaining the male and female populations at an optimal ratio without requiring a fish to leave the safety of the reef to find a mate. It also may be advantageous to keep the gene pool closed when the population is so highly adapted to a specific environment.

In reptiles with temperature-dependent sex determination, the extended duration of the maintenance period (during which temperature is sensed and the fate of the gonad can be reversed) could be a fitness strategy. The Charnov-Bull model postulates that temperature-dependent sex determination is adaptive when nest temperature favors the reproductive fitness of one sex over the other. In other words, female fitness is enhanced if female offspring develop under environmental conditions that improve female fertility. If the environment shifts to disfavor female reproduction, it may become advantageous to reverse the sex of the embryo to male.

The ability to undergo sex reversal attests to the incredible plasticity of the gonad. Sex reversal could be adaptive in animals with environmental sex determination and sex change is certainly a reproductive strategy in many fish. The persistence of sex reversal in mammals is difficult to explain because it nearly always leads to infertility, and therefore is presumed to be maladaptive. It is possible that sex reversal is a remnant of our evolutionary history or it may simply be a consequence of the bipotential nature of the gonad.

Where can I find out more?

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