DIVING INTO THE WORLD OF REGENERATION

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Some animals and most plants can regrow lost body parts. Why do some organisms regenerate, while others don't?

All of us have seen movies or heard stories of fights between gods and demons where hands or heads get severed, but grow back magically. In reality, humans do not have the ability to grow new hands or heads, but there are many organisms that do. The ability to regrow lost or damaged parts of the body is called **regeneration**.

Almost all regeneration occurs due to the presence of stem cells. Stem cells have the potential to 'become' any other kind of cell in the body through a process called differentiation. This process allows cells to perform specific functions. For example, the cells in our liver (called hepatocytes) are different from the cells in our heart (called cardiomyocytes). Hepatocytes cannot function as cardiomyocytes, and vice versa. Therefore, as you can imagine, the regeneration of the liver will require stem cells capable of differentiating into hepatocytes (see **Fig. 1**).

Regeneration can occur at many levels, ranging from the microscopic cell to the macroscopic body. For example, we lose nearly 200,000,000 skin cells every hour, but these cells are continuously replaced by new ones.[1] If a lizard on the wall loses its tail in an accident, it can regrow it. Its cousin, the axolotl, can regrow not only a new tail, but also new limbs, retina, and even parts of its brain and heart. The common earthworm, which we see emerging from the soil after the rains, also has some regenerative capacity. It may be evident from these and other observations (see **Examples I–V**) that not all organisms have the same regenerative capacity.

Regeneration in humans

At first glance, humans don't seem to have the regenerative capacities that amphibians and plants do. But keep in mind that regeneration can have a wide ranging definition.

On the one hand, the most common example of regeneration in humans is seen in the skin. Our skin cells are constantly being replaced, and our wounds getting healed (often without scars). On the other hand, the human liver can fully recover its

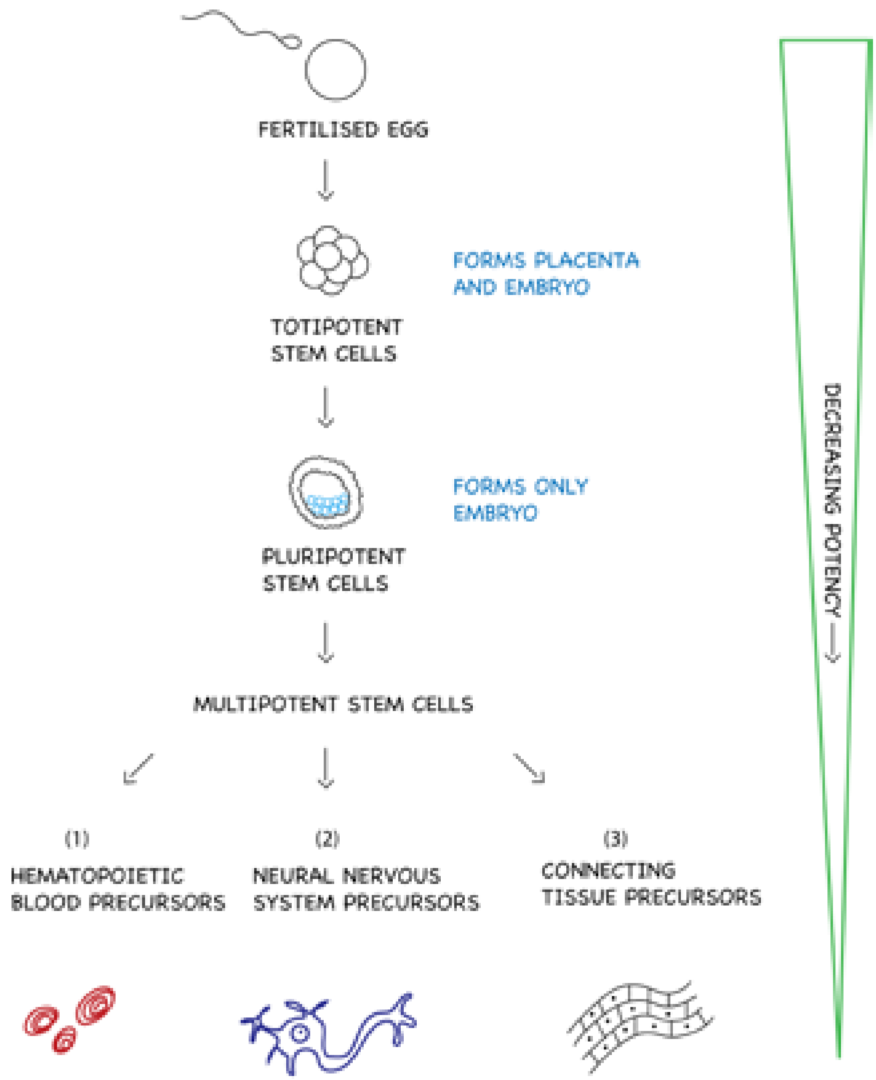

Fig. 1. Stem cells differentiate into various cell types. A fertilized egg divides to form a cluster of 'totipotent' stem cells. Each cell in this cluster has the potential to form all other cell types in the human body, as well as extraembryonic or placental cells. Some cell divisions later, these totipotent stem cells differentiate into pluripotent ones. Pluripotent embryonic cells can form any of the cell types in the human body except the placenta. Each pluripotent embryonic cell divides and specializes to form multipotent cells. Multipotent stem cells can develop into a limited number of cell types within a particular lineage. The different multipotent cells divide and differentiate into blood cells, neurons, muscle cells etc. Each of these can only grow into cells of their own kind.

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form and function from as little as one fourth of its original mass. In fact, this organ has the strongest regenerative ability in our body.

Why does this organ retain this ability, and not others? We don't have a complete answer to this question, but can take a guess by looking at the liver's regenerative capacity from an evolutionary perspective. As a detoxifier and regulator of blood glucose, ammonia, and lipid levels in the body, the liver is essential for the functioning of the brain and other essential organs. It also processes all circulation exiting the intestines, spleen, and pancreas. Consequently, the liver is prone to damage from chemical toxins and diseases. Left unchecked, this damage can result in liver failure. Not surprisingly, in most vertebrates, the liver retains its regenerative capacity — a capacity that is most likely to have been selected for in the hostile environment of our evolutionary past.[2]

While humans cannot match the regenerative capacities of an axolotl, the genes that give the axolotl the ability to regenerate parts of its brain and heart muscle also allow the regeneration of our fingertips. Yes, you read that correctly — up to a certain age, humans can replace relatively small amputations of a fingertip. A similar ability in mice depends on stem cells found under their nails. Since we share many regeneration genes with mice, it is likely that the same mechanism may be at play in humans.[3]

Parting thoughts

Regeneration in different organisms has mostly been studied by removing a body part (cells, tissues, limbs, organs etc.) and observing subsequent processes. As we develop increasingly sophisticated laboratory techniques, we are beginning to identify the genes and proteins involved in regeneration.

Apart from how awe-inspiring this process is, it may be useful to study regeneration in nature because:

1. Humans lose limbs due to accidents, infections, or even birth defects. Understanding the regenerative process at the level of genes, cells and organs across the plant and animal kingdoms is likely to yield useful insights for medical applications.

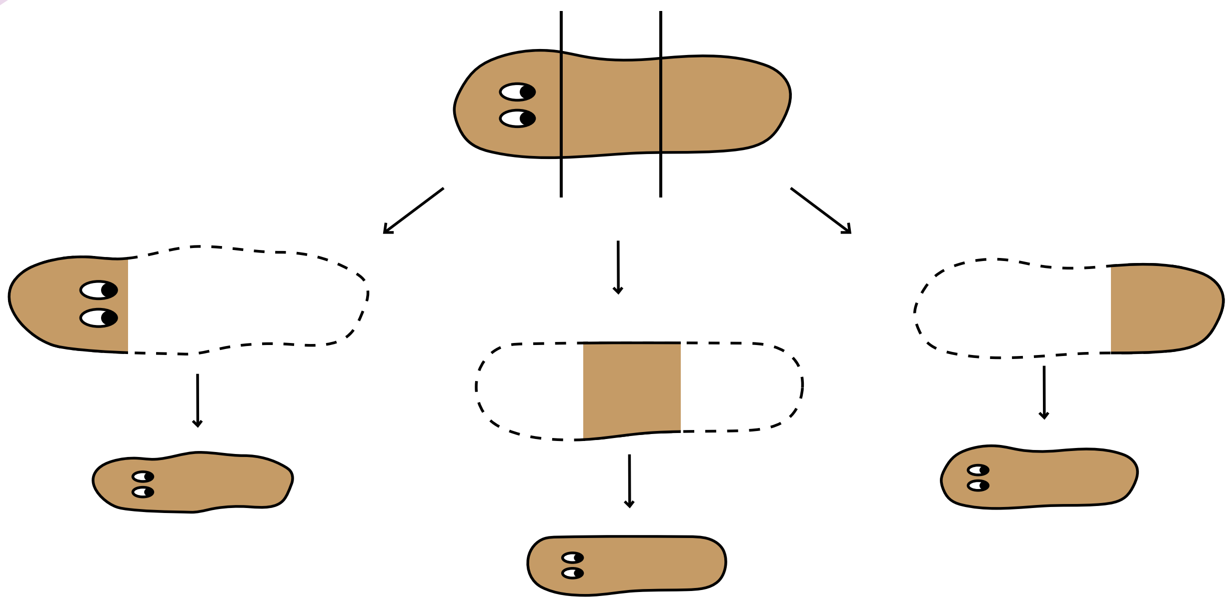
2. Regeneration is not very different from a dividing embryo — both processes involve the division of cells to form functional body parts. Since it is often difficult to study an embryo, capturing the process of regeneration offers us a window to understanding how embryos develop.

3. Studying organisms that have adapted their regenerative capacities to their environment can show us how such diversity has come about. It can also provide insights into the evolution of these organisms.

EXAMPLE 1: REGENERATION IN PLANARIA

Planaria is the common name for a group of flatworms with regenerative capabilities. For example, *Schmidtea mediterranea*, a flatworm found near the Mediterranean sea, is commonly used by scientists to study regeneration.

Within its brown, paper-thin body, this flatworm has a nervous, digestive, and reproductive system — sharing a lot in common with humans. However, unlike most organisms, not only do planaria survive after being cut into pieces, each piece can regrow into the whole functional organism! Each such regenerated organism is an exact replica of the original worm. What is even more surprising is that even a piece as small as $1/279^{th}$ of the initial worm can regenerate!



Planaria can regenerate from very small amputated fragments.

The stem cells in planaria that are responsible for this extraordinary capacity for regeneration are called neoblasts. When a flatworm is cut, neoblasts move towards the cut site, divide, and specialize to recreate the missing worm. But, how do the neoblasts know how much of the body is missing? How do they know whether the missing region is a head or a tail? We are still very far from answering these questions.

Read more here: Playing with wormies (2011). Baldscientist. URL: https://baldscientist.wordpress.com/2011/09/23/playing-with-wormies/.

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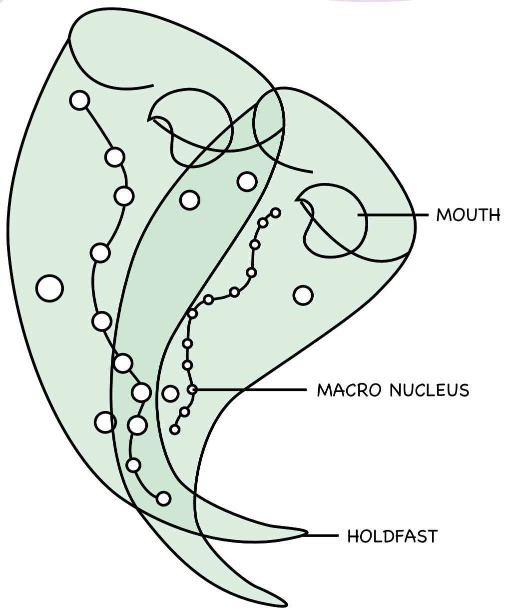
EXAMPLE II: REGENERATION IN *STENTOR COERULEUS*

Stentor Coeruleus was discovered by Abraham Trembley, an 18th century naturalist. It is a very large unicellular organism with remarkable regenerative properties. As unicellular organisms go, *S. coerules* is so huge that it is visible to the naked eye! With a length of about 1-2 mm, this blue-green organism's body is shaped like a 'shehnai' or 'nadaswaram'.

Stentor coerules is a large unicellular organism.



Any piece of the Stentor that contains a portion of its nucleus and cell membrane has the capacity to regenerate into a full organism.

The wider end of a Stentor contains its mouth regions with cilia (thin thread-like structures) that move water into its body. The Stentor feeds on the bacteria, algae, and other smaller ciliates in the ingested water. The other, narrower, end of the Stentor helps the organism attach itself to rocks and plants in water. Any piece of the Stentor that contains a portion of its nucleus and cell membrane has the capacity to regenerate into a full organism.

When we cut a planarian, we are cutting an organism with multiple cells. In contrast, when we cut a Stentor, we are cutting a single cell with almost 'tomatoish' consistency. How does the cell maintain its integrity after being cut? Why don't the cell's contents leak into the water around? These are questions that we don't have answers to yet.

Read more here: Slabodnick, M. M. & Marshall, W. F. Stentor coeruleus. Curr. Biol. CB 24, R783–R784 (2014). URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5036449/.

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EXAMPLE III: DO HYDRA LIVE IN YOUR NEIGHBOURHOOD?

The multicellular hydra also shows remarkable regenerative capacity, which is believed to be basis of its immortality! Hydra are usually found in freshwater ponds. If you live near a clean pond or stream that flows softly, and are equipped with a magnifying glass and a little patience, it may not be too hard to spot some of these ~1 cm creatures. One can find them attached to the underside of leaves and other vegetation. Try your luck — it is an interesting expedition for students and teachers alike. If you do find some hydra, store them in some filtered pondwater in a clear glass or plastic container.

The multicellular hydra shows remarkable regenerative capacity.

Credits: Neeharika Verma

Use a scalpel or blade to cut individual hydra at different positions along its body. Store the cut pieces in pond water in clear glass or plastic containers, and leave these in a cool place (18-24 °C). Observe the fragments every 24 hours. Record the following:

- Are there some parts that regenerate into functional organisms, and others that don't?
- Do all fragments regenerate at the same rate? Why would this happen?

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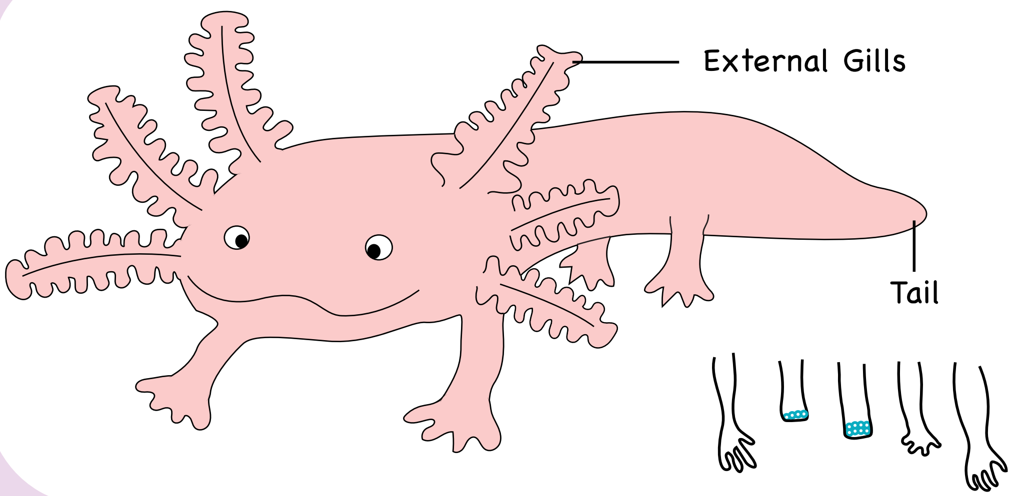
EXAMPLE IV: REGENERATION IN THE AXOLOTL *ABYSTOMA MEXICANUM*

The axolotl (pronounced ack-suh-lot-tul) is a salamander that looks a lot like the lizards we find in our homes, but is actually an amphibian that lives its entire life in water. Unlike most frogs that we know, the axolotl remains at the larval stage, never metamorphosing to an adult.

The axolotl can regenerate many of its body parts, including its limbs, spinal cord, heart, even parts of its brain, without forming any scar tissue whatsoever. It can also receive transplanted organs (anything from eyes to limbs) without rejecting them. Imagine if humans had the ability to recover from spinal cord injuries in the same way? The permanent larvae-like stage of the axolotl could be one reason for the axolotl's impressive regenerative capacities — they just don't really ever 'grow up'. After all, the regenerative capacities of many species, including humans, are much stronger in their early stages of growth and development, and are lost over time.



A sketch of axolotl, with external gills. Inset: Form develops gradually as cells divide (blue) and the morphology of a regenerated limb returns to its original state.

Native to lakes in and around Mexico city, axolotls have become highly endangered in the wild, largely due to pollution arising from urbanization. Funnily enough, since they can be grown in captivity, axolotls are reared around the world as both household pets and model organisms in scientific laboratories. Not being able to study them in the wild makes it difficult for us to understand how their environment has shaped their evolution. Many scientists are currently investigating the genetic basis of the axolotl's regenerative capacity — interestingly, the axolotl's genome is much larger than that of humans.

Read more here: (1) Biology's beloved amphibian — the axolotl — is racing towards extinction. URL: https://www.nature.com/articles/d41586-017-05921-w.
(2) Regeneration: The axolotl story. Scientific American Blog Network. URL: https://blogs.scientificamerican.com/guest-blog/regeneration-the-axolotl-story/.

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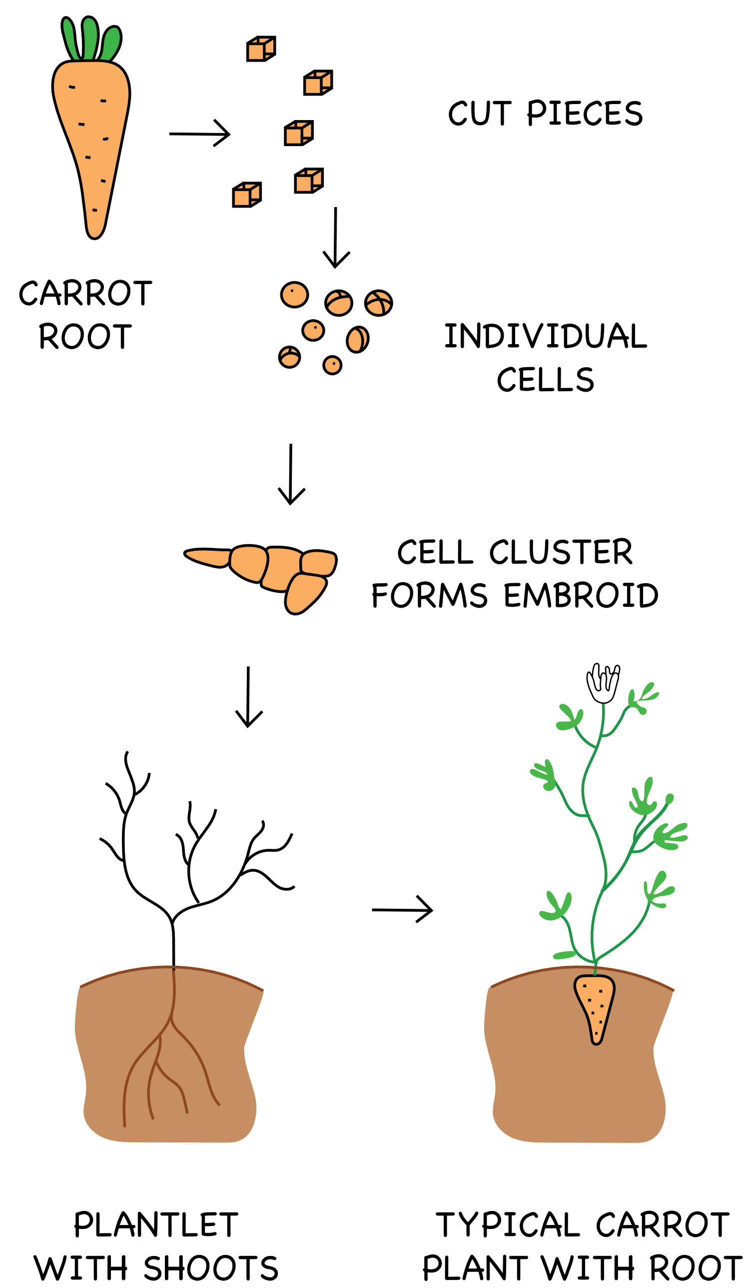
EXAMPLE V: REGENERATION IN PLANTS

It may not be an exaggeration to say that regeneration in plants is far more versatile than that in animals. In fact, in 1958, Frederick Steward from Cornell University showed that a whole carrot plant could be regenerated from a single cell derived from the phloem of the plant. While this is an extreme example, we regularly see plant cuttings develop shoots and roots when placed in a moist environment.

Often regeneration is seen as a process in which the organism has a fixed set of instructions on how the body should look (this is called the body plan). Therefore, if a portion of the body is lost, regeneration must involve a return to its original shape, size, and function. However, this definition does not hold true for the plant kingdom, because most plants don't have a fixed body plan! This is something we may all see in our day-to-day interactions with plants. Break off a leaf from a plant, and it may not be replaced in the same way a limb is replaced in animals. But, the plant will survive, compensate, and adapt to a new body plan. What is most fascinating is that a leaf may, in many plants, sprout roots and become another plant — much like how planaria regenerate!



An entire carrot plant can be regenerated from single isolated phloem cells.

PTO

TRY THIS OUT!

Many plants provide a readily available experimental system that even children can use to study different aspects of regeneration. These include common houseplants such as aloe vera (*Aloe barbadensis*) and the money plant (*Epipremnum aureum*), as well as outdoor shrubs such as lantana (*Lantana camara*) and touch-me-nots (*Mimosa pudica*).

To identify plant parts that can regenerate by producing roots or shoots, encourage students to choose one of these species for study. It may be useful to keep a set of control plants, and another set of plants for experimentation. Students could amputate some or all of the roots, leaves, apex, or even branches of a plant by systematically removing them with a sharp instrument. Ask students to record the proportion of plants that survive and recover from each type of amputation.

Similarly, to study the effect of environmental factors on regeneration, conduct the same experiment under varying conditions of temperature, moisture content of soil, etc.

These exercises will encourage students to think about the following:

- Do all plants have the same regenerative capacity?
- Which amputations do plants find it easier to recover from?
- What environmental conditions are required for regeneration?

Read more here: Steward Experiment and Application of Totipotency (2014). Biology Discussion. URL: http://www.biologydiscussion.com/plants/steward-experiment-and-application-of-totipotency/5832.

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Learning more about the different mechanisms for regeneration used in the animal world could help us replicate this process in humans too. We have already made a lot of progress in this field. For example, we have identified stem cells in multiple human tissues. By inducing these cells to grow into different cell types, we are able to produce organ and tissue replacements to damaged parts in humans. While many mysteries about regeneration remain, with ever-increasing knowledge, we might just be able to imagine a day when we can grow back an amputated head, like the demons from many Indian stories!

Key takeaways

- Regeneration is the capacity to regrow a lost body part, and recover a function.
- Regenerative capacity varies across the plant and animal kingdom. Some organisms can regenerate cells, others can regenerate full organs.
- Investigating regenerative capacity is possible even at the school level by studying simple invertebrates and plants.
- Gaining an understanding of regeneration has applications in medicine and developmental biology.

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