

Then, in the early fifties, the World Health Organization launched the most ambitious and expensive international programme in history to eradicate smallpox once and for all. After many vicissitudes and no little heroism on the part of the workers sent into remote and hostile territories, the objective was accomplished amidst much jubilation. September of 1977 saw the last recorded case of naturally transmitted smallpox on the planet. But the Glynn's' invigorating story ends on a sombre note: just as smallpox had been viewed as a weapon thrust by providence into the hands of colonialists to exterminate indigenous peoples — instructions for its dissemination even appear in official documents — so the cold-warriors of the twentieth century were not slow to spot its possibilities. In a laboratory at Zagorsk, only fifty miles from Moscow, were stored 20 tons of a particularly virulent strain of the smallpox agent, and there is evidence that the work of preparation and testing did not proceed without accidents. (In Kirov, further east, a like quantity of the plague bacillus was amassed.) Genetic engineering offered the even more alluring prospect of a hybrid virus of smallpox and Ebola, and many other clever innovations. The stocks in Zagorsk were reportedly destroyed after the collapse of the Soviet imperium, but who knows what cultures are even now being brewed in clandestine laboratories around the world? Certainly smallpox vaccine is being stockpiled in the West against a day of reckoning. All this and a great deal more is absorbingly related in this fine book, which encapsulates so much of man's intellectual lustre, self-sacrifice and physical heroism, and his folly, obduracy and villainy — a very microcosm of human history.

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Quick guide

Planarians

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What are planarians? As any high school student will tell you, planarians are flat, free-living worms, members of the phylum Platyhelminthes (Platy, flat; helminth, worm) with cross-eyed-looking photoreceptors and a remarkable capacity for regeneration (Figure 1). The regenerative prowess of planarians has been known for centuries: Dalyell wrote in 1814 that planarians appear to be “immortal under the edge of the knife”.

What is the smallest fragment that can regenerate a complete worm? According to T.H. Morgan, a lateral fragment 1/279th the size of the original worm. This corresponds to about 10,000 cells. If you consider that such a small fragment now has the job of re-specifying its body midline to regain bilateral symmetry, while simultaneously preserving anteroposterior and dorsoventral polarities and resetting these axes to their appropriate positional values, it is easy to see why planarians have captured the imagination of generations of biologists.

What happens when you starve a planarian? They degrow! Yes, they get smaller, not by shrinking the size of their cells, but actually by losing cells. Such ‘degrowth’ obeys allometric rules of scale and proportion, and occurs without noticeably compromising the animal's form and function.

How do planarians reproduce? The capacity of planarians for regeneration is familiar, yet less is known about their internal anatomy, modes of reproduction, cell biology and embryogenesis. Even though planarians are devoid of a coelom, they have derivatives of all three germ layers — ectoderm, mesoderm and

endoderm — organized into complex organ systems (Figure 2). They reproduce sexually or asexually. Sexual animals are hermaphrodites unable to self fertilize, while asexual animals undergo transverse fission posterior to the pharyngeal opening. The embryogenesis of freshwater planarians is equally intriguing: cleavage of the fertilized egg was described as ‘anarchic’ by early developmental biologists. No overt gastrulation or epiboly has been described in these embryos, yet they manage to develop anteroposterior and dorsoventral axes without difficulty. Not bad for an animal usually regarded as ‘simple’.

So, why are they not one of the major model species? This is somewhat of a puzzle. The planarian literature reads like a ‘Who's Who’ of biology. Not only do we find Cuvier (1817) perplexing over planarian phylogeny, but Darwin reported on specimens he collected in Brazil while aboard *H.M.S Beagle*. Planarians are also mentioned in Weismann's influential book ‘*The Germ Plasm*’ (1892), and they were the subject of at least 12 papers by Morgan. In ‘*Whatever Happened to Planaria?*’ (1992), Mitman and Fausto-Sterling concluded that the absence of planarians in modern developmental biology is likely a historical accident driven more by personalities than by real biological limitations. Their scholarly interpretation of the history of planarian biology in the 20th century is compelling, as we now know that planarians are not only easy to rear and manipulate surgically, but are also accessible to molecular dissection.

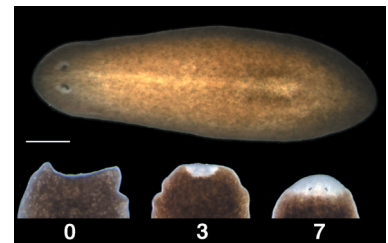


Figure 1. The planarian *S. mediterranea* (top) and three stages of head regeneration (bottom). The numbers are days after amputation. (Scale bar, 650 μm .)

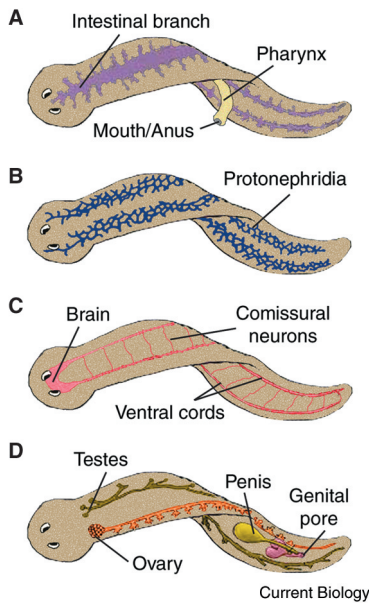


Figure 2. The anatomy of a planarian. (A) The gastrovascular system consists of one anterior and two posterior gut branches. (B) The excretory system is a dorsal network of canals with specialized cells known as flame cells. (C) The central nervous system. (D) The reproductive system. Testes and ovaries are found on both sides of the animal but are shown here only in opposite sides for clarity.

Why was *Schmidtea mediterranea* chosen as a model planarian? There are thousands of planarian species, but not a lot is known about them and some have only been described once. From the onset, I wished to identify and develop as a model system a species amenable to molecular studies. Such species should be diploid, with a relatively small genome, robust regenerative properties and the ability to reproduce sexually and asexually. *S. mediterranea* fulfilled all of these criteria, and for the past six years Phillip A. Newmark and I have endeavored to develop this species as a model system in which to address long-standing problems of biology, such as regeneration and stem cell regulation.

What are neoblasts? Small, highly undifferentiated cells with large nuclei and very little cytoplasm, distributed throughout the body of an adult planarian. They are the only mitotically active cells in planarians, and so are responsible for the cell

proliferation observed in both intact and amputated animals. They constitute 25–30% of all planarian cells, and have been shown to differentiate into epidermis, muscle, neurons and germ cells, among others. Self-renewing neoblasts are regarded as stem cells and are being used to identify and test mechanisms that regulate stem cell activities in metazoans.

What can planarians tell us about ourselves? Given the degree of conservation between planarian and human genes, the exploration of planarian biology should contribute to understanding human biology. Like mammals, planarians do not segregate their germ cell lineage during early embryogenesis; rather, germ cells are formed from stem cells post-embryonically. Planarians should thus facilitate analysis of the mechanisms by which cell–cell interactions specify germ cell fates. Despite the importance of tissue homeostatic processes to human biology and health (humans are estimated to lose ~10 billion cells per day), relatively little is known about how tissue homeostasis is controlled. Adult planarians constantly replace their tissues during normal cell turnover, so they provide an experimental paradigm in which to study such homeostatic processes. The long lifespan of planarians and the way they use stem cells to replace aged tissues should aid the identification of genes that regulate the rate at which cells are lost through cell death, and those that promote longevity by controlling cell replacement. Finally, the robust and complex behavioral responses of planarians to stimuli, combined with modern methodologies for studying gene function, means that planarians should be a good system for studying the neural control of learning, memory, social behavior, chemotaxis, rheotaxis and geotropism.

What tools are available for studying planarians? The past six years have seen a significant increase in our ability to interrogate the biology of

planarians at the molecular level. We now have at our disposal clonal lines, whole-mount *in situ* hybridization protocols (pioneered by Kiyokazu Agata and his laboratory in Japan), large collections of non-redundant cDNAs, microarrays and loss-of-function assays, including RNA interference. The development of BrdU and fluorescence-activated cell-sorting protocols to label, follow, and purify neoblasts have begun to shed light on the cell biology of the planarian stem cells.

Is there a planarian genome project? Yes, the genome of *S. mediterranea* was prioritized for sequencing by the National Human Genome Research Institute in March of 2003 and is currently underway at the Genome Sequencing Center in Washington University, Saint Louis.

Where can I find out more?

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