<Further Development 8.1>

Haeckel's Invagination and Metchnikoff's Ingression

In the 19th century, Ernst Haeckel hypothesized that gastrulation occurs through an ancestral *invagination* mechanism by which a portion of an epithelium folds inward without the participating cells losing tight adhesive connections. The primary early evolutionary purpose of these invaginating cells was/is to become internalized and form the primitive gut and ultimately the tissues for feeding. In constructing his theory, Haeckel conducted many comparative observations of the embryonic anatomy across phyla that included sponges, worms, amphibians, and mammals among many others (**FIGURE 1**). It was not until a fortuitous trip to study sponges in Norway however, that Haeckel collected an undescribed marine, multicellular ball of ciliated cells (Reynolds and Hülsmann 2008; Levit et al. 2021). He named this organism *Magosphaera planula*, and attempted to describe from both observation and imagination the peculiar life cycle of this potential protozoan (Haeckel, 1870). Although *M. planula* exhibited free-swimming unicellular and ameoboid stages, Haeckel recounts how it transitioned into an egg phase that experienced cleavages and formed a blastulalike sphere as an adult (**FIGURE 2A**). While neither *M. planula* nor an organism like has ever been discovered since, it was the living validation Haeckel felt he needed to support his invagination theory (Livet, et al. 2021; Reynolds and Hülsmann, 2008). His discovery of this blastulalike protozoan paired with his comparative observations of diverse embryos reaffirmed his theory of the evolution of gastrulation by way of an extinct but ancient common ancestor—the Gastraea. Most important was Haeckel's declaration that this common gastrulating ancestor exhibited the hallmark morphogenic behavior of invagination.

Haeckel's hypothesis of an ancestral invagination mechanism met significant criticism, especially from Élie Metchnikoff, a famous immunologist turned embryologist and evolutionary biologist. Metchnikoff spent much time studying the anatomical life cycles of cnidarians (jellyfish) and echinoderms (seastars and sea urchins). From these observations, Metchnikoff theorized that the gut forming endoderm evolved gradually from morphogenesis of cells that subsequently phagocytosed food particles; he called this the Phagocytella Theory (**FIGURE 2B**; Metchnikoff, 1886). This behavior—*ingression*—is characterized by a change in morphology from an epithelial to a migratory or mesenchymal cell property (i.e., an epithelial to mesenchymal transition). Ingression leads to cell movement out of the epithelial layer in which they resided and in the context of gastrulation, results in their migration into the interior of the embryo.

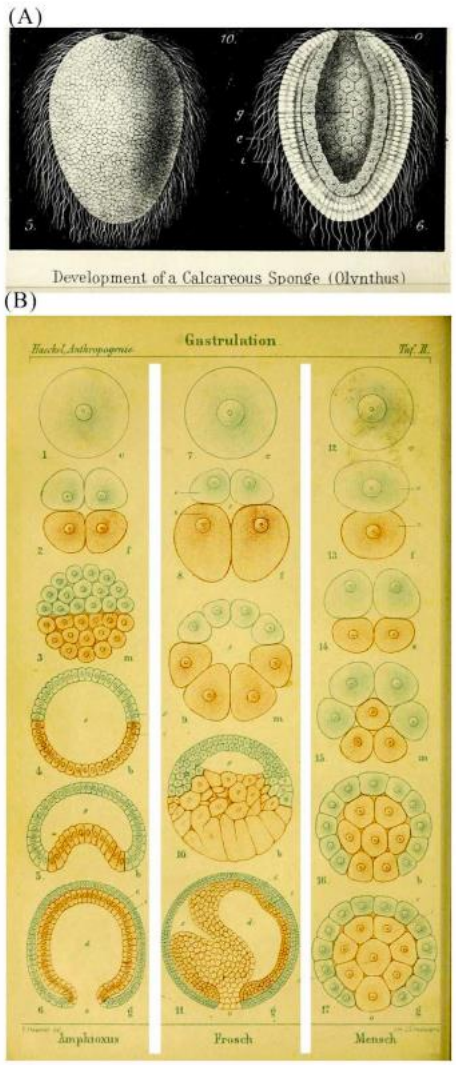

FIGURE 1 Gastrulae as drawn by Ernst Haeckel in the 19th century. (A) Surface and cross-sectional renderings of an early sponge embryo. (B) Side-by-side comparison of the progressive stages of embryogenesis from zygote to gastrulation (top to bottom) in amphioxus (left), frog (center), and human (right). Such studies led Haeckel to postulate that gastrulation movements were driven by an invagination mechanism. (From Haeckel 1876, 1877.)

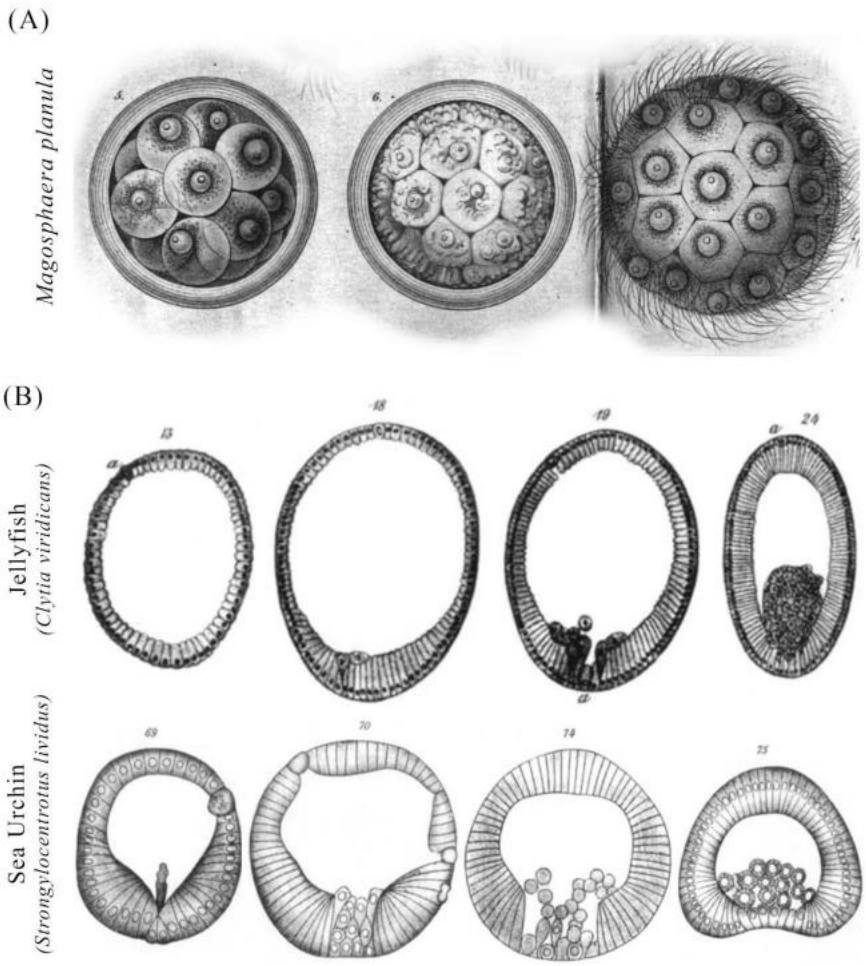

FIGURE 2 Drawings by Ernst Haeckel and Élie Metchnikoff of organisms in support of their differing theories of gastrulation. (A) Haeckel's rendition of the organism he called *Magosphaera planula*. Seen from left to right are the progressive stages of cleavage reaching the blastula-like adult stage that Haeckel felt validated his theory of an invagination mechanism of gastrulation. (B) Cross-sectional drawings by Metchnikoff of a jellyfish and a sea urchin that detail successive moments of cell ingression from the vegetal epithelium occurring in both animals. (A from Haeckel 1870, reprinted in Reynolds and Hülsmann 2008; B from Metchnikoff 1886.)

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