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The significance of Ethel Browne's research on *Hydra* for the organizer concept

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ABSTRACT

This article focuses on the roots of the organizer concept, which was developed by Hans Spemann during his studies of early embryonic development in amphibians. The fundamental properties of this axis-inducing signaling center have been elucidated through pioneering molecular research by Eddy De Robertis' laboratory and other researchers. Evolutionary comparisons have disclosed the presence of this signaling center, involving the interaction of Wnt and TGF-beta signaling pathways, existed not only in vertebrates but also in basal Metazoa such as Cnidaria. – Notably, even prior to the groundbreaking experiments conducted by Hilde Mangold and Hans Spemann, Ethel Browne conducted similar transplantation experiments on *Hydra* polyps. They were performed under the guidance of Thomas H Morgan and in the laboratory of Edmund B Wilson. Howard Lenhoff was the first to draw connections between Ethel Browne's transplantation experiments and those of Spemann and Mangold, igniting a vivid debate on the precedence of the organizer concept and its recognition in Nobel Prize considerations. This review critically compares the experiments conducted by Spemann and Mangold with those preceding their seminal work, concluding that the organizer concept clearly builds upon earlier research aimed at understanding developmental gradients, such as in the simple model *Hydra*. However, these approaches were not pursued further by Morgan, who shifted his focus towards unraveling the genetic control of development in flies, an approach that ultimately revealed the molecular identity of the Spemann organizer in vertebrates.

1. Introduction

The organizer concept has not lost any actuality and fascination since it was formulated by Hans Spemann a century ago based on the studies, he performed together with his graduate student Hilde Mangold nee Pröscholdt on early amphibian development (Spemann and Mangold, 1924). These studies were the culmination of a field of research that, in addition to Hans Spemann (1869–1941), was shaped by a whole generation of experimental embryologists, including Oskar Hertwig (1849–1922), Richard Hertwig (1850–1934) Wilhelm Roux (1850–1924), and Hans Driesch (1867–1941), Edmund Beecher Wilson (1856–1934), Theodor Boveri (1862–1915), Thomas Hunt Morgan (1866–1945). At the beginning of their scientific careers, these researchers were influenced by questions of comparative anatomy and descriptive embryology, but they were all finally striving to decipher the mechanisms of development and regeneration by the influence of Ernst Haeckel (1834–1919). A major part of their results was obtained through transplantation experiments in which the morphogenetic properties of a specific tissue were tested.

Spemann was awarded the Nobel Prize in Physiology or Medicine in 1935 for his discovery of the organizer effect in embryonic development, two years after Morgan's accolade for his work on the role of chromosomes in heredity in 1933. What is less well known is that the Morgan laboratory also worked quite intensively on the mechanisms of induction including research employing the freshwater polyp *Hydra* as an experimental system (Holstein, 2022). One of the students working together with Morgan was Ethel Browne who published a paper entitled "The production of new hydranths in hydra by the insertion of small grafts" (Browne, 1909). While recognized in the scientific community during the twenties, a discussion about the extent of Ethel Browne's contribution to Spemann's Nobel Prize has lingered since Lenhoff's essay in 1991 (Lenhoff, 1991). Here, the role of Ethel Browne was classified as rather marginal, especially in the essays by Klaus Sander in his excellent series "Landmarks in Developmental Biology" and in a book reviewing Spemann's research by Peter E. Fäßler (Fäßler, 1997; Fässler and Sander, 1996; Sander and Faessler, 2001). Is this justified and relevant? This essay will give a re-assessment of Ethel Browne's contribution in the light of its historical perception and against the

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backdrop of recent molecular data on the organizer concept.

2. Spemann and the history of the organizer concept

Spemann's work has been described and phrased by Victor Hamburger (1900–2001) in his inspiring and beautiful book "The Heritage of Experimental Biology – Hans Spemann and the Organizer" (Hamburger, 1988). In the foreword to his book, Hamburger stated that he "entered Spemann's Zoological Institute at the University of Freiburg in 1920 together with Hilde Proescholdt-Mangold, the co-discoverer of the organizer, and Johannes Holtfreter, who was to become Spemann's most original and most productive student – and my lifelong friend." Alike Hamburger, Hans Spemann has begun his scientific carrier in Heidelberg (1891–1893) where his interest in experimental developmental biology was awakened. He visited Theodor Boveri at Würzburg University. Boveri was founder of the chromosomal theory of inheritance, together with Walter S. Sutton (1877–1916), one of E.B. Wilson's graduate students (Tagarelli et al., 2003). Spemann decided to perform his doctoral thesis with him and the two had a lifelong friendship (Hamburger, 1988; Spemann, 1936; Spemann, 1943), even though his thesis work did not lead him directly to the organizer project. Building upon Boveri's chromosome work on *Ascaris*, Spemann was to examine another nematode in his thesis (Spemann, 1895) and submit a comparative anatomical thesis as habilitation work which was required to receive a professorship in Germany (Spemann, 1898).

Still in Boveri's laboratory, Spemann carried out his first experiments on amphibian embryos (Fäßler, 1997; Hamburger, 1988), which were related to previous experiments of Driesch, who had previously utilized sea urchins as a model to demonstrate the regulatory potential of early blastomeres, a concept disputed by Roux (Hamburger, 1988). To test the nuclear equivalence of the blastomeres, Spemann performed his famous "constriction experiments" on fertilized newt eggs (1901–1904). Eggs were constricted with a fine hair at different time points and positions along cleavage planes and the embryo's body axes. Through this approach, he demonstrated the nuclear equivalence of the blastomeres from 2-cell stage to 16-cell stage embryos (Spemann, 1901a; Spemann, 1902; Spemann, 1903; Spemann, 1936). Spemann also confirmed and extended Morgan's earlier findings according to which the distribution of cytoplasmic factors in the eggs had a dramatic effect on the outcomes of these experiments. If the constriction plane aligned with the future median plane of the embryo body (splitting the gray crescent (Hamburger, 1988) twins were obtained; otherwise, "belly pieces" lacking dorsal structures were observed (Spemann, 1902). Further supporting these classical experiments, De Robertis demonstrated that even a bisected blastula, cut with a scalpel blade, could yield identical twins if both fragments retained Spemann's organizer tissue (De Robertis, 2006).

Ablation and transplantation experiments on lens formation in eye development in frogs (1901–1908) were Spemann's next step towards the organizer (Hamburger, 1988). These experiments addressed directly the phenomenon of induction and can therefore be considered a precursor of the organizer experiment (Fäßler, 1997; Hamburger, 1988; Sander and Faessler, 2001). – Today, the molecular mechanisms of lens induction by the optic vesicle of the optic nerve have been clearly shown to depend on the competence of the ectodermal tissue to respond to the inductive signals of the optic vesicle including Bmp4 and Fgf signaling (Gilbert, 2014). Spemann discovered that after ablating the optic rudiment from embryos of *Rana fusca* no lens formation occurred (Spemann, 1901b; Spemann, 1912; Spemann, 1918). This was not confirmed for other frog species (King, 1905; Mencl, 1903), but finally solved by Warren H. Lewis, who transplanted the optic vesicle from *Rana palustris* beneath non-lens ectoderm of *Rana sylvatica*, which then underwent lens differentiation in the host tissue (Lewis, 1904; Lewis, 1907; Sander and Faessler, 2001). This was clearly the first experiment designed to define an embryonic inductive interaction (Grainger et al., 1992; Sander and Faessler, 2001) suggesting inductive signals from donor tissue.

The history of lens induction shows that Spemann's ablation and transplantation experiments were not the starting point in the experimental analysis of position-dependent pattern formation as emphasized by Victor Hamburger in 1988 (Hamburger, 1988): "The general themes of '*dependent differentiation*' which had been formulated by Roux in the 1880s, and of embryonic induction were in the air. In fact, in theoretical matters, some of Spemann's contemporaries were already further advanced than he. I think particularly of Driesch and his friend Curt Herbst. Following a series of brilliant experiments on sea urchin eggs, Driesch in 1894 (at the age of 27) had elaborated a sophisticated '*analytical theory of organic development*' in which the role of the nucleus and cytoplasm, inducing chemical stimuli, and other fundamental problems and mechanisms were discussed with great lucidity. It should be noted that Driesch, known to biologists as the proponent of vitalism, was at that time a mechanist. His conversion to vitalism did not occur until 1898 (Driesch, 1951). Herbst, who deserves credit as the first practitioner of chemical experimental embryology –made some notable discoveries in his studies of the effects of ions on sea urchin development – and published his theoretical work on '*Formative Stimuli in Animal Ontogeny*' in 1901, the same year in which Spemann's first study appeared. It is an extensive and systematic survey of developmental mechanisms. A crucial issue in the approach of both Driesch and Herbst is well formulated by the latter: '*to establish the occurrence of formative stimuli which are exerted from one part of the embryo to another, and to determine eventually the possibility of a complete resolution of the entire ontogenesis into a sequence of such inductions*' (Herbst, 1901b)." The influence of Driesch's pioneering experiments with sea urchins on the emerging field of experimental embryology can therefore not be overstated, notwithstanding debates on priority issues, such as Driesch vs Haeckel (De Robertis, 2009; Sánchez Alvarado, 2008; Sánchez Alvarado and Yamanaka, 2014).[1] Driesch and Herbst had an intensive exchange of ideas with many researchers including Morgan and Wilson with whom Driesch shared a life-long friendship (Driesch, 1951; Hamburger, 1988) (see below).

For Spemann, his time in Würzburg, with the constriction and transplantation experiments was very successful. As a result, he was offered for a full professorship for zoology in Rostock, which he accepted in 1908. Later, in 1914, he received an even more prestigious position as the division head for *Entwicklungsmechanik* at the newly founded Institute of Biology of the Kaiser Wilhelm Gesellschaft (KWG) in Berlin-Dahlem (now Max Planck Gesellschaft, MPG). After World War One, in 1919, Spemann moved to Freiburg, where he accepted the prestigious

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[1] It was argued recently that Haeckel had first discovered the totipotency of embryonic cells / blastomeres in a publication on the development of siphonophores (Cnidaria) (De Robertis, 2009; Sánchez Alvarado, 2008; Sánchez Alvarado and Yamanaka, 2014) and that Driesch had not cited his doctoral supervisor in any of his papers (Richards, 2008; Sánchez Alvarado, 2008). This is wrong in two respects. In his work, Haeckel was cutting (planula) "larvae of the second day", i.e., larvae older than one day and clearly after cleavage (see *Zur Entwicklungsgeschichte der Siphonophoren*, page 73–79, plate VI, Figure 36, and plate XI, Figure 73–76 (Haeckel, 1869). And then, Driesch refers to Haeckel's work in the first sentence of his following publication on "Theory of Pattern Formation in Animals" (Driesch, 1893a) preceding his better-known 1894 book on the same subject (Driesch, 1894), with a remarkably clear statement on priority and intention of Haeckel and his work (Driesch, 1893a): "Before I turn to the actual subject of these lines (…) a duty of historical justice must be fulfilled. It has only recently become known to me by chance, and is probably also unknown to other circles, that Haeckel in his *Development of Siphonophores* (1869) reports experiments which are identical in subject matter to those carried out by Roux [13 | (Roux, 1888)], Chabry [2 | (Chabry, 1887)], Wilson [17 | (Wilson, 1892)] and myself [4–7 | (Driesch, 1891; Driesch, 1892a; Driesch, 1892b; Driesch, 1893b)]. Haeckel divided blastulae of *Crystalloides* with the aid of needles into pieces of unequal size (in 2, 4, or 4); in a short time, each isolated piece closed into a full small sphere by tilting its edges together and developed at least one air sac, if it was very small; if it was larger, however, several or all organs or individuals of the siphonophore species. This result is therefore in fully consistent with the experiments carried out by Chabry, Wilson and myself on eggs of Ascidia, *Amphioxus* and Echinidae, and therefore, although the experiments have been carried out more or less crudely and without emphasizing the essential aspects, more as a minor matter, Haeckel should be named as the first developmental mechanists experimenter, regardless of the bad treatment he has recently given to the entire science by completely misunderstanding its intent." (translation by TWH, cited references included).

chair held by Weismann until 1914. This period is described by Victor Hamburger, who began, along with Hilde Pröscholdt in 1920 his thesis with Spemann (Hamburger, 1988). Hilde Pröscholdt later married Otto Mangold who had begun his thesis with Spemann in Rostock, completed it in 1919 and later became division head of the Institute for Biology (KWG) in Berlin. This period was also described by Otto Mangold and the Swiss Fritz Baltzer, whose mentors were Boveri and Spemann (Baltzer, 1962; Mangold, 1953).

3. Hilde Mangold and her thesis on the "Induction of Embryonic Primordia through Implantation of Heterologous Organizers" in newts

The key experiment that defined the organizer in amphibians (*Triton* sensu *Triturus*) was the transplantation of the upper (dorsal) blastoporal lip of a gastrula of a non-pigmented donor (*Triturus cristatus*) into the presumptive gastric (ventral) region of the gastrula of a pigmented host (*T. taeniatus* or *T. alpestris*) at the onset of gastrulation (Spemann and Mangold, 1924) (Fig. 2a,b). This induced an "unitary organization of the secondary embryo and the chimeric structure of the secondary axial organs, that is, their composition of donor and host cells" (Hamburger, 1988). The outcome of this experiment was that the notochord was unpigmented, i.e., it consisted of transplanted cells, while the neural tube consisted almost entirely of pigmented host tissue (Hamburger, 1988; Spemann, 1936) as beautifully documented in a microphotograph taken 1993 by Klaus Sander (Fig. 2c) (Sander and Faessler, 2001).

A crucial aspect of Spemann's key work on the organizer concept is that it is based on the dissertation work of Hilde Mangold, which was submitted as a joint publication with Hans Spemann as first author. This complicates the assessment of individual contributions to this remarkable piece of work which has been discussed in detail in several publications (Fäßler, 1997; Fässler and Sander, 1996; Hamburger, 1988; Sander and Faessler, 2001). Utilizing Hilde Mangold's original laboratory notes, Fäßler reconstructed the data basis of Mangold's doctoral thesis (Fäßler, 1997; Fässler and Sander, 1996). According to this, a total of 259 transplantations were carried out with *Triturus cristatus* as the donor and *T. taeniatus* or *T. alpestris* as the host. Among these, a total of 73 transplants (28 %) survived, and axial induction – i.e., the formation of an ectopic neural tube and other structures, was found in 26 chimeras (36 %), with *T. taeniatus* as host alone accounting for 43 % (Fässler and Sander, 1996). The embryos of *T. cristatus* were primarily chosen as donor for the experiments as they were more sensitive than the pigmented species. However, in the chimeras recognizing the non-pigmented cells of the donor in a pigmented host proved to be more challenging (Fässler and Sander, 1996) (Fig. 2c). The high mortality rate of *T. cristatus* embryos (50 % in the tailbud stage) can be attributed to a balanced lethal system (Wallace, 1994; Wielstra, 2020).

It should be noted that only six grafts out of 26 were included in Mangold and Spemann's 1924 publication (e.g., Fig. 2a) (Fässler and Sander, 1996). The reasons for this are unclear, but it has been speculated that issues of polarity and positional information may have been addressed in the remaining transplants (Fässler and Sander, 1996). Questions of co-authorship in connection with the doctoral thesis may also have been relevant, as this publication was the formal document of Hilde Mangold's doctoral achievement (Fässler and Sander, 1996).

Criticism of the organizer experiments of Spemann and Mangold has so far focused mainly on the sample size and experimental details (Gimlich and Cooke, 1983; Jacobson, 1982; Jacobson, 1984) as well as on the broader question of whether Mangold and Spemann were really the first to demonstrate the organizer effect. While the experimental details have been commented before (De Robertis, 2009; Fäßler, 1997; Fässler and Sander, 1996; Hamburger, 1988; Sander and Faessler, 2001), the question of prioritization is more than "a cocktail party question"(Fässler and Sander, 1996). – Two approaches have been discussed here: The work of Lewis on transplantation of the blastopore lip in frogs (Lewis, 1907) and the work by Ethel Browne in *Hydra* (Lenhoff, 1991). Although Lewis conducted a similar experiment to Mangold and Spemann by transplanting the dorsal and lateral lip of the blastopore of *Rana palustris* (Lewis, 1907), he was ultimately unable to make a statement on induction. This was because transplantation was homoplastic, unlike his extensive experiments on lens induction previously, where he used heteroblastic transplants (*R. palustris* and *R. sylvatica*). In those experiments he conclusively demonstrates the induction of the lens by the optical vesicle (Lewis, 1904; Sander and Faessler, 2001). The lingering question pertains to Ethel Browne's experiments with *Hydra* (Browne, 1909), which, according to Lenhoff, should have been taken into account when awarding the Nobel Prize to Spemann in 1935 (Lenhoff, 1991).

4. Thomas H. Morgan and Ethel N. Browne's work on axis induction in *Hydra*

Ethel Nicholson Browne (1885–1965) published her seminal paper on axis induction, titled "*The Production of New Hydranths in Hydra by the Insertion of Small Grafts*," in 1909 when she was a graduate student. In this work, she demonstrated the induction of a secondary body axis in the host organism through the grafting of small tissue fragments. Although Child cited this work repeatedly in the context of his gradient theory (Child, 1947), it was Howard Lenhoff who, in 1991, played a crucial role in revitalizing the attention given to Browne's contributions within the biological community (Lenhoff, 1991).

Ethel N. Browne pursued her studies at Columbia University (1906–1913), obtaining a master's degree in zoology in 1907 (Butler, 1967). She commenced her scientific career in the laboratories of E.B. Wilson and T.H. Morgan, who were both in the Department of Zoology at Columbia University. She conducted her initial experimental work on Morgan's suggestion **[Footnote 2]**,[2] while her dissertation was then under Wilson and focused on the chromosomes and spermatogenesis of *Noctonecta* (Hemiptera) (Browne, 1909; Browne, 1910; Browne, 1913). Following the completion of her doctoral thesis, Browne married the physiologist E.N. Harvey in 1916. Subsequently, her research predominantly concentrated on the development of sea urchins and she contributed significantly to the field with numerous foundational papers addressing the cell and developmental biology of sea urchins (Harvey, 1956).

It is remarkable that a publication predating the famous Mangold-Spemann work by fifteen years disclosed a similar organizer phenomenon in the simple freshwater polyp *Hydra.* Ever since Abraham Trembley's pioneering work (Trembley, 1744), *Hydra* and other cnidarians have stood as favored models for researchers exploring developmental processes in embryogenesis and regeneration. Among these influential researchers, T.H. Morgan played a pivotal role. While his genetic experiments on chromosomes, inspired by the rediscovery of Mendel's work, laid the foundation for the field of genetics (Morgan, 1915a-c), Morgan was also a pioneer in the study of regeneration (Morgan, 1901). Morgan's keen interest in the regeneration of planarians and cnidarians revolved around the fundamental question of how a regenerating organ could maintain or alter its identity based on axial position. He shared this interest with Driesch, who was also working on the embryology of ctenophores (Driesch and Morgan, 1895) and regeneration of hydrozoans (Driesch, 1896).

Morgan's work on regeneration in cnidarians was focused on the fresh water polyp *Hydra* (Fig. 3) and the marine colonial hydrozoan *Tubularia,* together with several graduate students (King, 1901; Morgan, 1901; Peebles, 1897; Peebles, 1900; Whitney, 1907). A significant undertaking in the laboratory of Morgan was the development of a method

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[2] "During the winters of 1906–1908, I carried on some experiments in grafting *Hydra viridis* for the purpose of throwing more light on the factors concerned in regeneration. The work was done at the suggestion of Professor Morgan, whom I sincerely thank for his kind interest and support" (Browne, 1909)

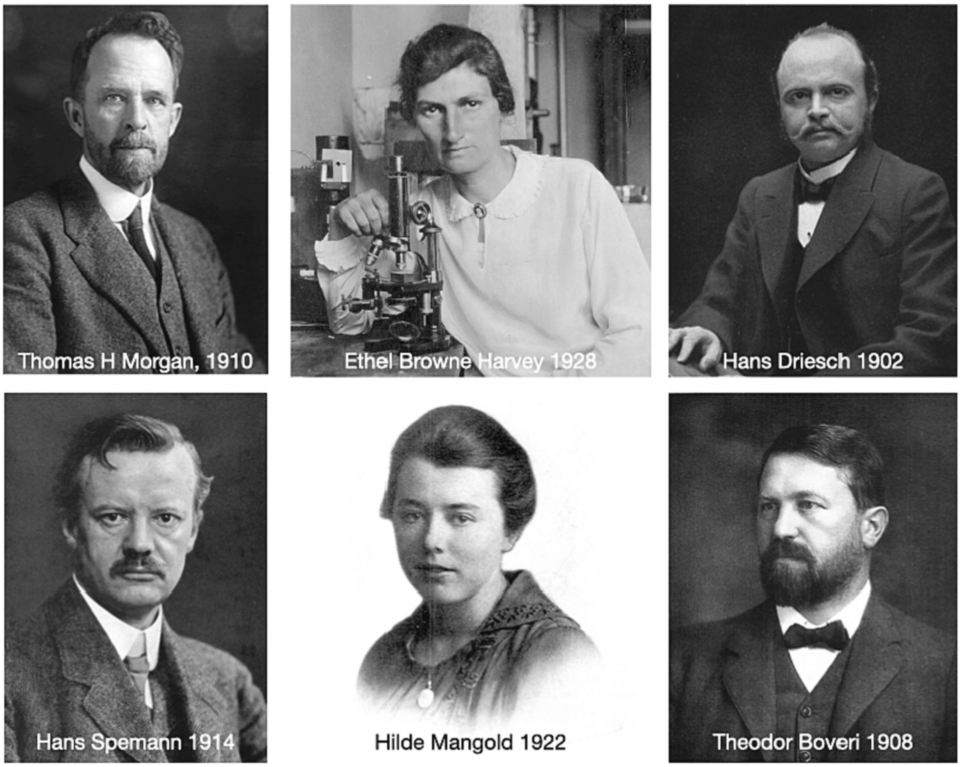


Fig. 1. Leading figures involved in the emergence of the organizer concept. Thomas Hunt Morgan (1866–1944) suggested to Ethel Browne (1885–1965) to carry out the induction experiment with transplants of an aposymbiotic and symbiotic strain of the green *Hydra* (*Hydra viridissima*). Hans Spemann (1869–1941) initiated and supervised Hilde Mangold's (1898–1924) dissertation project on the organization experiment with transplants of various *Triturus* species that differ in the pigmentation of their eggs. Hans Driesch and Theodor Boveri had a great influence on Morgan and Spemann and were decisive for the emergence of experimental embryology and genetics. **Sources**: **Th.H. Morgan**, Marine Biological Laboratory (Woods Hole, Mass.) https://history.archives.mbl.edu/digital-collection/thomas-hunt-morgan-columbia-university; **E. Brown-Harvey**, Marine Biological Laboratory (Woods Hole, Mass.) https://history.archives.mbl.edu/digital-collection/ethel-browne-harvey; **H. Driesch**, (Driesch, 1951), Wikimedia common; **H. Spemann**. (Spemann, 1943); **H. Mangold** (Fässler, 1996) Int. J. Dev Biol. 40, Fig. 8.; **T. Boveri**. Wikipedia common. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

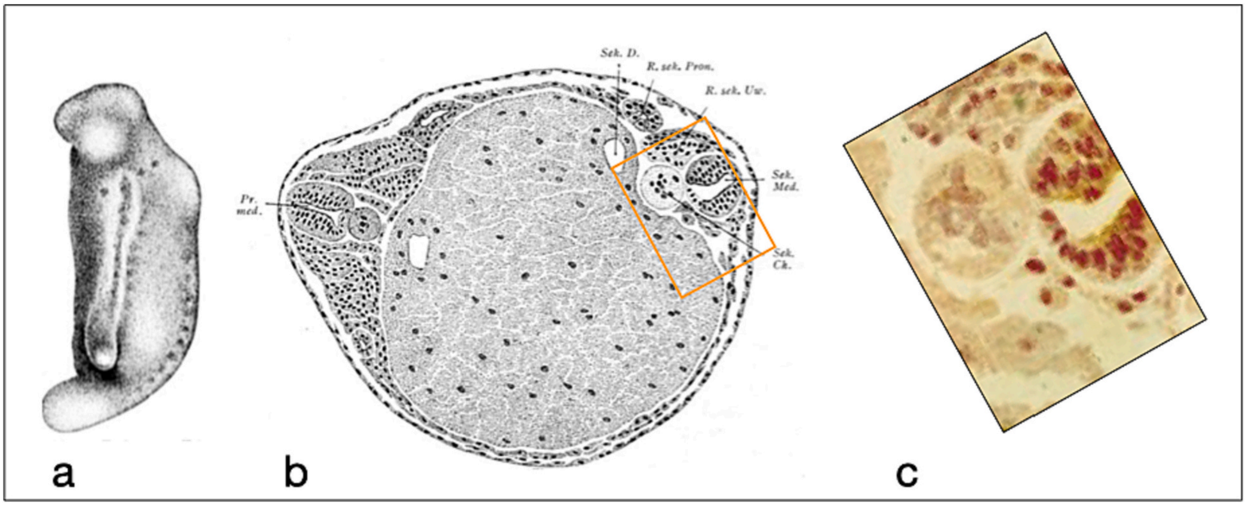


Fig. 2. Outcome of transplantation experiment UM 132b by Hilde Mangold. (**a-b**) The dorsal blastoporal lip of a *Triturus cristatus* embryo was transplanted to a gastrula of *Triturus taeniatus* (Spemann and Mangold, 1924); (**c**) is a corresponding photomicrograph of the secondary anlagen, which was taken in 1993 by Klaus Sander. It shows the melanin granules marking the pigmented host cells (*Triturus taeniatus*; best seen close to the neural lumen); the transplant cells of *Triturus cristatus*, three of them located in the floor plate, are less pigmented than those of the host (Sander and Faessler, 2001). **Sources**: (**a**) Spemann and Mangold (1924), Fig. 21, taken from Spemann (1936), Fig. 79; (**b**) Spemann and Mangold (1924), Fig. 24, taken from Spemann (1936), Fig. 80; (**c**) Sander and Faessler (2001), Fig. 11B (Courtesy Embryological Collection, Hubrecht Laboratory, Utrecht/NL).

distinguishing donor and graft tissue in transplantation experiments. While several experiments demonstrated successful grafts within the same species, attempts with polyps from different species proved unsuccessful (Peebles, 1897; Wetzel, 1895). Early transplantation experiments were carried out with *Hydra viridissima*, a species that harbors endosymbiotic *Chlorella* algae in its endoderm epithelial cells (Fig. 3a,

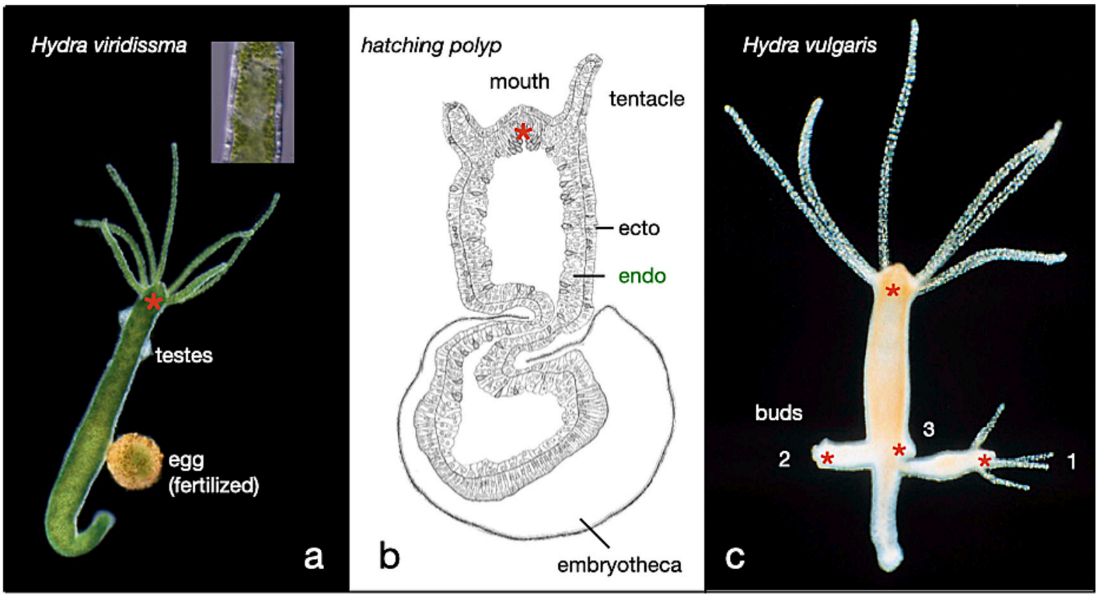


Fig. 3. *Hydra* polyps and their development. *Hydra* can reproduce sexually (**a-b**) and asexually by budding (**c**). (**a**) Hermaphroditic polyp of *Hydra viridissima* (Schuchert, 2010) with testes and eggs in the gastric region;inset shows tentacle harboring endosymbiotic *Chlorella* algae in the endoderm and an algae-free ectoderm. (**b**) Embryos form a theca, from which a primary polyp hatches after diapause (Brien, 1965; Schuchert, 2010). Note the gastrula-like shape of the polyp with an outer ectoderm, an inner endoderm, and a mouth that corresponds to the blastopore in free living planula larvae (Maegele et al., 2023). (**c**) Asexual budding occurs at the boundary of the gastric region to the peduncle (budding zone) and buds continuously form (numbers) and detach from the mother polyp (Clarkson and Wolpert, 1967; Otto and Campbell, 1977). The head organizer in *Hydra* (Broun and Bode, 2002; Broun et al., 2005; Hobmayer et al., 2000; Technau et al., 2000) corresponds to the hypostomal region (red star). **Sources**: (**a**) Schuchert (2010), Fig. 46; inset is an original interference contrast micrograph; (**b**) Brien (1965), Fig. 45; (**c**) Fig. S1A (Nüchter et al., 2006). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

inset), and behaves and regenerates like the common brown *Hydra* (Fig. 3b, c) (Rand, 1899a; Rand, 1899b). The use of polyps with different amounts of algae allowed a crude distinction between host and donor (King, 1901), but it was not until Whitney succeeded in producing endosymbiont-free polyps of *Hydra viridissima* that the differentiation between host and donor became possible, allowing unprecedentedly precise cellular resolution (Whitney, 1907).

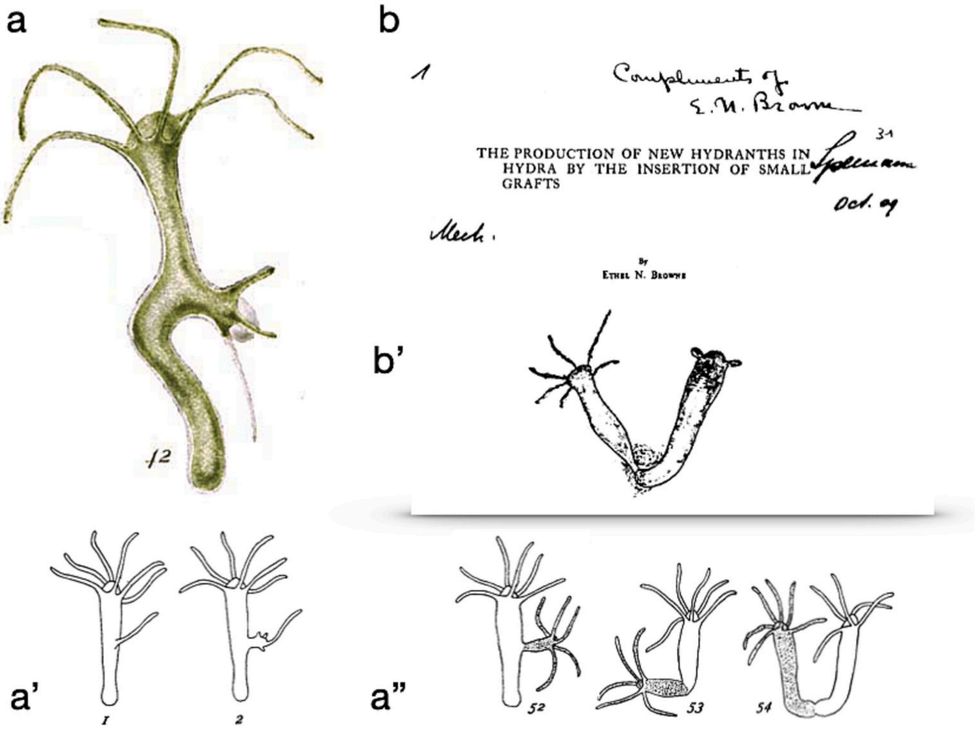
It was Whitney's success in producing algae-free polyps of *Hydra viridissima* that made Ethel Browne's induction experiment possible and one can speculate that this was the reason why Morgan recommended his talented student to carry out the key experiment. For this purpose, a piece of the hypostome of a polyp without algae was removed and this white tissue transplanted into the gastric body wall of another *Hydra viridissima* polyp carrying algae (green). She found that the green hypostomal tissue induced a new hydrant of the algae free host tissue here (Fig. 4a). Within a few days, a second hydrant developed with mouth and tentacle (Fig. 4a'). This new hydrant was clearly not a bud, because it did not form any basal disk ("foot") like any bud, which is able to detach from the parent within 2 to 3 days of formation (Otto and Campbell, 1977). Thus, it is genuinely an induced secondary body axis and the hydrant therefore remained permanently attached to the parental body column. This tissue was passively pushed towards the foot by the tissue flow of the of constantly dividing tissue (Campbell, 1973). Detachment only occurred by a kind of longitudinal splitting (Fig. 4a"). The process of axis induction in *Hydra* has been replicated in numerous studies, also in a modified form, to test gradients of head activation and inhibition (Li and Yao, 1945; MacWilliams, 1983a; MacWilliams, 1983b; Mutz, 1930; Webster, 1966a; Webster, 1966b; Webster, 1967; Webster and Wolpert, 1966; Wolpert et al., 1972; Yao, 1945a; Yao, 1945b) The experiment is so simple that it can be easily carried out in any practical course for students.

In summary, both organizer tissues are functionally very similar, as the hypostomal region of a polyp of *Hydra* and other cnidarians corresponds to the blastopore of their embryos (Fig. 3c). Despite the much simpler morphology of *Hydra* polyps, the remarkable similarity between the two experiments demonstrates the non-autonomous nature of the organizer and its ability to form axes (see below).

5. Whimsical twists

Were Spemann or Mangold aware of the *Hydra* experiments that came from Browne and Morgan before they began their experiments? As explained by Lenhoff (1991), the close parallels between the experiments of Browne (1909) and the Nobel Prize experiments of Spemann and Mangold (1924) are evident. Both papers demonstrated that tissue taken either from the hypostome region of *Hydra* or from the dorsal primordial lip of *Triturus* embryos, when transplanted into an ectopic region (here gastral or presumptive gastral region), can influence (induce) the adjacent host tissue. This induction leads to the formation of a secondary polarity axis that corresponds to the primary polarity axis. Notably, there is no growth or reorganization of the transplanted tissue; rather, it is the host tissue that is induced by the donor tissue. In Browne's experiment, it is obvious that signals from the pigmented tissue must influence the neighboring, non-pigmented tissue (Fig. 4a). In the experiments of Mangold and Spemann, the situation was complicated by the necessity of using different species with distinct pigmentation.

Victor Hamburger has appended a section titled *"Hilde Mangold: Co-Discoverer of the Organizer"* to his book Heritage of Experimental Biology (Hamburger, 1988). In this section, he was adding some "whimsical twists" to underscore the significance of Hilde Mangold's contributions to the organizer and provides personal insights into the project's



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Compliments of
E.N. Browne

THE PRODUCTION OF NEW HYDRANTHS IN
HYDRA BY THE INSERTION OF SMALL
GRAFTS

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Spemann
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By
ETHEL N. BROWNE

Fig. 4. Browne's and Mangold's *Hydra* experiments. (**a**) A piece of the hypostome with a tentacle taken was grafted from an aposymbiontic polyp of *Hydra viridissima* to the gastric region of a polyp of *Hydra viridissima* whose endosymbiotic algae had not been removed; taken from (Browne, 1909). (**a'**) and (**a''**) show scheme of the experiment and outcome of the induced secondary body axis (labeled) that move with tissue flow to the foot end without separation from the host tissue demonstrating that it is not a bud (Browne, 1909). (**b**) Cover page of the reprint of Browne's, 1909 paper found in Spemann's reprint collection (Lenhoff, 1991). (**b'**) Drawing out of Mangold's lab book on 4th March 1921, showing two polyps that were about to separate (Sander and Faessler, 2001), which looks similar to Browne's experiment shown in (**a''**). **Sources**: (**a**) Browne (1909), Fig. 42; (**a'**) Browne (1909), Figs. 1 and 2; (**a''**) Browne (1909), Figs. 52–54; (**b**): Lenhoff (1991), Fig. 8; (**b'**) Sander and Faessler (2001), Fig. 9 (Embryological Collection, Hubrecht Laboratory, Utrecht/NL).

initiation (Hamburger, 1988).[3] He explains how Hilde Mangold began her dissertation with a *Hydra* experiment originally described by Trembley in 1744, involving the inversion of the ectoderm and endoderm of *Hydra's* gastric column, akin to turning the finger of a glove inside out (Trembley, 1744). While it is feasible to separate and recombine both germ layers between different animals (Epp et al., 1986; Epp et al., 1979; Kishimoto et al., 1996; Murate et al., 1997; Smid and Tardent, 1982), the challenge lies in altering the fate of ectodermal and endodermal epithelial cells. Given their distinct stem cell lineages (Holstein, 2023) this has not been possible so far. – Hamburger's fascination with this experiment led him to explicitly inquire with Pierre Tardent, renowned for his work on cnidarian development and particularly of *Hydra* and *Tubularia* (Tardent, 1978), while working on his book about the organizer around 1982 (when I was an postdoc assistant with Pierre Tardent). As Hamburger describes the situation (Hamburger, 1988), Hilde Mangold could not replicate this experiment with *Hydra*, which then became the starting point of her organizer project with *Triturus*.[3] Notably, when her thesis work was published in 1924, Spemann insisted on being the first author of the publication, departing from the general practice of allowing graduate students to publish their work as single authors.[3]

Hamburger's commentaries have left a lasting impact on subsequent texts discussing Mangold's biography, e.g., Lenhoff, Fäßler and Sander (Fäßler, 1997; Fässler and Sander, 1996; Lenhoff, 1991; Sander and Faessler, 2001). It is likely that Mangold conducted additional *Hydra* experiments, possibly including the organizer experiment. Sander and Fäßler presented a drawing from Mangold's lab book depicting a graft resembling a successful, albeit late, graft with two hydrants on the verge of separating through longitudinal splitting (Fig. 4b', 4a"; see above) (Sander and Faessler, 2001). This suggests that Hilde Mangold may have attempted to repeat Ethel Browne's experiments when beginning her thesis in Spemann's group.

Spemann, possessing Ethel Browne's reprint and handwritten commentary on her using the term "induction", must have been well aware of Browne's work (Lenhoff, 1991) (Fig. 4b). Despite the predominant and criticized use of the term "formation" in the paper, rather than "induction" (Fässler and Sander, 1996; Sander and Faessler, 2001), the experimental design, employing clearly labeled tissue to demonstrate its influence on the formation of similar structures in ectopic tissue, is so focused on the process of induction that debates over terminologies seem more semantical. Notably, there are no direct references to Browne's work in Mangold's thesis (Spemann and Mangold, 1924) or in any other of Spemann's earlier or subsequent publications, including his influential Silliman Lectures given in Yale in 1933 (Spemann, 1936). Although a later work on *Hydra*, largely based on Browne's *Hydra* research (Mutz, 1930) and titled "Transplantation experiments on *Hydra* with special consideration of induction, regionality and polarity" is listed in the references, was is not mentioned in Spemann's text (Spemann, 1936).

In summary, there's a compelling likelihood that Spemann and Mangold were aware of the Browne's experiments on *Hydra* and following Morgan's suggestions. Various claims that Browne's contributions were minor (Lenhoff, 1991) can be effectively refuted. Browne's experiment was groundbreaking, with both she and Morgan recognizing the profound significance of induction experiments, even if they did not explicitly used the term organizer.[4] Although it is true that the Bauplan of a vertebrate is much more complicated than that of a *Hydra*, it is the gastrula, the first important stage of embryogenesis, to which the body structure of a *Hydra* corresponds.

6. Impact of genetics on decline and rise of the organizer concept

Spemann and Morgan were part of the same age group and emerged as the most influential figures in experimental developmental biology. However, they approached their work from distinct perspectives. Morgan, driven by a deep interest in marine biology, frequented the Zoological Station in Naples (1890–1902) and crossed paths with Driesch. Driesch's sea urchin experiments (see above) were most influential for Morgan and ultimately led to transplantation experiments to gain a better understanding of developmental processes. Morgan was also captivated by Trembley's discovery, prefacing his own book on regeneration with a description of that famous experiment involving the cutting of a polyp in half (Morgan, 1901).

On Morgan's side, there was a strong interest in unraveling the underlying mechanisms, exemplified by efforts to interfere with Ca^{2+} or Li^{+}, as demonstrated by Driesch's colleague and friend Curt Herbst for sea urchin development (Herbst, 1897; Herbst, 1900; Herbst, 1901a; Herbst, 1904). However, delving into biochemical and cell biological mechanisms proved challenging due to the limited molecular knowledge of that time. Therefore, when the power of the chromosomal theory of inheritance became clear through the initial work of Boveri, Sutton, and Wilson, Morgan shifted his full attention to the genetic approach and redirected his research towards genetic studies on *Drosophila*, despite his lifelong interest in regeneration biology (Sturtevant, 1959; Sunderland, 2010). Morgan's pivot, along with E.B. Wilson, marked a turning point in experimental biology towards genetics in the early 20th century (Holstein, 2022; Sunderland, 2010). This may explain why Morgan did not pursue this field of research after the publication of Browne's *Hydra* paper, and did not cite this work in later publications even though its experiments were carried out in his laboratory. Instead, his interest in Mendelian heredity and his genetic experiments on chromosomes (Morgan, 1914; Morgan, 1915a; Morgan, 1915b; Morgan, 1915c;

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[3] "The story of Hilde Proescholdt's dissertation would not be complete without recounting some whimsical twists. While practically all of Spemann's students were given problems dealing with the early development of amphibians, Spemann made an exception with Hilde. His thoughts had turned back to one of his famous predecessors in experimental zoology, the French amateur naturalist Abraham Trembley. In the late eighteenth century Trembley had discovered the amazing power of regeneration of the freshwater polyp, *Hydra*. He had cut the animal into small pieces, and each of them had regenerated a complete polyp. Among the many ingenious experiments, he had performed was one that eventually the outer lining of the body was transformed into the lining of the intestinal tube and vice versa. The interchangeability of the two layers had a parallel: the transplantation experiments of Otto Mangold had shown the same interchangeability of inner and outer germ layers nearly amphibian embryos. Apparently, Spemann had then become interested in checking on Trembley's claim, and he had suggested to Hilde Proescholdt that she repeat the inversion experiment. She set out to do so. Despite her considerable skill and perseverance, she was not successful. Even the help of the master of microsurgery himself was of no avail; the two of them tried to hold the inverted hydra in place with a fine glass rod, but the uncooperative creature always managed to uncurl. In the meantime, the relatively short breeding season of the amphibians had advanced (methods for inducing egg laying by hormone treatment were not yet available), and Proescholdt became impatient. Spemann accommodated her and turned over to her an experiment that had a high priority on his agenda: the transplantation of the upper lip of the blastopore of an early gastrula to the flank of a gastrula of another species. With beginner's luck, she obtained in early May an embryo which displayed on its flank a large secondary neural tube. Spemann-and everybody else in the lab- oratory-was impressed, and this one case was reported in a brief postscript dated May 1921 to a Spemann publication of the same year that dealt with transplantations between species (obviously a related topic). The term 'organizer' was introduced and defined in this postscript. But it took Proescholdt another breeding season to complete her thesis work. The results were written up jointly by the two authors; the paper was submitted to Roux's Archiv in June 1923 and it appeared in print in 1924. – Hilde Proescholdt, who in the meantime had become Mrs. Mangold, was not happy that Spemann had added his name to her thesis publication, while Holtfreter and I and all the rest of us saw ourselves proudly in print as sole authors. Moreover, Spemann had insisted on having his name precede hers! But Spemann was perfectly right in claiming precedence, while she apparently did not fully realize the significance of her results. It was not granted to her to live to see the great impact her experiment had on the course of experimental embryology." (Hamburger, 1988)

[4] Howard Lenhoff (1991) also referred to Dr. Sears Crowell, a long-time hydroid researcher at the MBL, who made the following remark about Ethel Browne Harvey, also repeated in a letter (Lenhoff, 1991): "We met by chance as she was leaving the MBL (Marine Biological Laboratory) building where she was giving a lecture. Out of the blue, she said, '*You know it was me who first discovered the organizer*'. That was not an exact phrase. I replied that I knew that was indeed the case …"

Morgan, 1915d) laid the foundation for his Nobel Prize-winning work and for the establishment of genetics, with which his name is primarily associated today.

By comparison, Spemann pursued a divergent path. Although his highly esteemed doctoral father Theodor Boveri – whom he dedicated his book on a theory of development (Spemann, 1936) – was a co-founder of the chromosome theory of development and thus of genetics, Spemann did not share the same enthusiasm for the subject of his thesis to continue working on it. Instead, he focused his work on the construction and transplantation experiments. During her time in the Morgan lab, Ethel Browne concluded her *Hydra* experiments, marking the conclusion of Morgan's era in experimental embryology. Simultaneously, Spemann had just completed his work on lens induction. He received his position as a full professor in Rostock (1908), then moved to Berlin (1914) and finally Freiburg (1919), where he established his new group together with Otto Mangold culminating in the organizer project (Fäßler, 1997; Hamburger, 1988) (see above).

It should also be emphasized that Ethel Browne's work was not ignored at all in the field of experimental embryology. As mentioned above, the German Elfriede Mutz at Marburg University has repeated Browne's experiments on *Hydra* (Mutz, 1930), and Browne's work was much appreciated by Charles Manning Child (1869–1954). Child was professor at the University of Chicago and at Marine Biological Laboratory, Woods Hole. He was aware of the equivalence of Browne's experiment with the Spemann-Mangold organizer experiment.[5] For Child, induction was not restricted to amphibian development, but was a general phenomenon in animal embryogenesis and regeneration that certainly also did occur in such simple systems like cnidarians and planarians (Child, 1941). Child wanted to mechanistically understand long range-phenomena in development and was therefore working with the hydrozoans *Hydra* (Child, 1947; Child, 1948; Child and Hyman, 1919) and *Tubularia* (Child, 1907). Child's work on gradients directly led to the most influential work by Alan Turing (Turing, 1952), Lewis Wolpert (Hicklin et al., 1969; Wolpert, 1969; Wolpert et al., 1972), and Gierer and Meinhardt (Gierer et al., 1972; Gierer and Meinhardt, 1972) in the last 50s to early 70s. But understanding induction phenomena at the biochemical level and particularly the Spemann's organizer effect in amphibians proved to be extremely challenging and frustrating, leading to a decline of interest and publications on the subject even in the post-war period (De Robertis, 2009). Thus, the molecular nature of the organizer effect remained elusive for a long time.

One successful path was the search for inductive and neurotrophic factors (Hamburger, 1980). Here, Victor Hamburger's work on dorsal root ganglia in chick embryos along with his guidance of Rita Levi-Montalcini in her initial experiments was ultimately leading to the isolation of Nerve Growth Factor (NGF) (Cowan, 2001; De Robertis, 2009; Hamburger, 1980; Levi-Montalcini, 1987; Oppenheim, 2001).

The other path, however, followed the genetic route, tracing back to Bovery, Wilson, and Morgan. Fundamental advancements in genetics, particularly the discovery of DNA's structure, provided a framework to explore the molecular basis of heredity, paving the way for novel genetic approaches to study development. This initially led to the first genetic linkage map of *Drosophila* by Alfred H. Sturtevant (1891–1970) (Sturtevant, 1913), who was a graduate student of Morgan, and finally, to the identification of the genetic control of early embryonic development in *Drosophila* by Lewis, Nüsslein-Volhard, and Wieschaus (Lewis, 1978; Nusslein-Volhard and Wieschaus, 1980), for which the Nobel Prize was awarded in 1995, six decades after Morgan and Spemann. It became also possible to clone highly evolutionarily conserved *Drosophila* genes in vertebrates, such as the *Hox* genes (Carrasco et al., 1984; McGinnis et al., 1984), revealing unexpected evolutionary conservation of genes across phyla. Ultimately, comprehensive search of the genes acting in gastrulation and the organizer of vertebrates became possible, as demonstrated in the pioneering work of De Robertis and colleagues (Cho et al., 1991; De Robertis et al., 1992; De Robertis and Sasai, 1996; Niehrs et al., 1994; Sasai et al., 1995; Sasai et al., 1994).

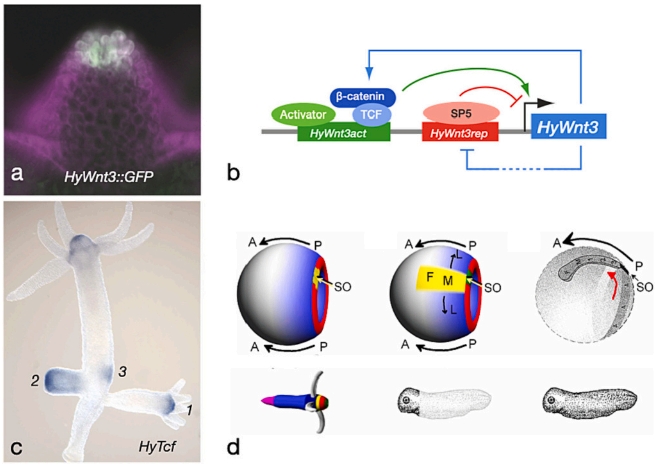

Fig. 5. Axis formation in hydra and vertebrates. (**a-c**) The head organizer of *Hydra* is characterized by Wnt signaling that controls the oral-aboral body axis. *Wnt3* (**a**) and other *Wnt* genes are expressed in hypostomal epithelial cells forming an autocatalytic signaling center (**b**) with co-expressed *Tcf* (**c**), *β-catenin* and *brachyury* (Hobmayer et al., 2000; Holstein, 2022; Lengfeld et al., 2009; Nakamura et al., 2011; Technau et al., 2000; Vogg et al., 2019*)*. (**d**) Hans Meinhardt's model, according to which the oral-aboral axis corresponds to the posterior-anterior body axis in vertebrates (Holstein, 2022; Meinhardt, 2012; Niehrs, 2010). Accordingly, the marginal zone in vertebrates with *brachyury* and *Wnt* (red) corresponds to the hydra head organizer. The schematic on the right shows that in vertebrates this is the source of Wnt signaling that drives anteroposterior determination of the future brain region in a gradient-like manner as shown before (Kiecker and Niehrs, 2001). The chordin-based Spemann organizer (SO, yellow) is located in the marginal zone, which corresponds to the ancestral hydra-type organizer. In vertebrates, cells originating from the organizer in the marginal zone form the prechordal plate (yellow) of the future head region, which acts as a midline organizer (L-M-L) and initiates neuronal development in the overlying ectoderm. It has been postulated that this mechanism creates a Cartesian-like coordinate system that structures the anterior-posterior and dorsal-ventral axes in chordates (Meinhardt, 2012), see also Niehrs (2010). Accordingly, the vertebrate trunk could be an intercalation between hydra's trunk and oral end with high levels of neurogenic *Nkx-2* (pink) and *otx* (blue) characteristic for the vertebrate brain (Meinhardt, 2012). **Sources**: (**a**) Nakamura et al. (2011), Fig. 2B; (**b**) Holstein (2022) Fig. 4b, modified from Nakamura et al. (2011), Fig. 6; (**c**) Hobmayer et al. (2000), Fig. 2A; (**d**) Meinhardt (2012), Fig. 12. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

7. Evolutionary links between the *Hydra* and the vertebrate organizer

Advances in comparative genomics have enabled the analysis of the molecular nature of the *Hydra* head organizer. Surprisingly, it was discovered that the hypostomal region of *Hydra* and other cnidarians acts as a Wnt signaling center (Fig. 5a-c). *T cell factor* (*Tcf*) and *β-catenin* are strongly upregulated and *co*-expressed not only in steady-state polyps but also during budding and head regeneration (Fig. 5c) (Hobmayer et al., 2000; Technau et al., 2000). They act in an autocatalytic signaling center with activating and inhibiting signals (Fig. 5b). Comparative genomics also revealed that cnidarians already possess the complete Wnt gene repertoire known from chordates and vertebrates

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[5] "It was shown by Browne (1909) and confirmed by later workers that even small pieces of *Hydra* from the region about the base of the tentacles, implanted laterally, can persist and determine new apical regions and polarities, largely from host tissue; that is, the implant is dominant and acts as an inductor. Similar small pieces from other regions of the body are incorporated in the body wall or resorbed" (Child, 1941)(page 378)

and insects suggesting that they already evolved in the common prebilaterian ancestor (Kusserow et al., 2005)). The common and primary function of Wnt signaling is likely in gastrulation. The Wnt pathway acts at the site of the blastopore, defining the polarity of the primary body axis in cnidarian embryos (Holstein, 2012; Holstein, 2022; Holzem et al., 2024). In *Nematostella* it has been beautifully demonstrated that the blastoporal lip can be transplanted and act as an organizer (Kraus et al., 2016; Kraus et al., 2007). Thus, blastoporal tissue in cnidarians and chordates/vertebrates possesses the same morphogenetic capacity and uses the same molecular mechanism – that is Wnt/β-catenin signaling – for inducing and patterning the primary body axes (Kraus et al., 2016). These findings also demonstrate that the organizer activity discovered by Ethel Browne in adult *Hydra* polyps is not a phenomenon of regeneration, but based on a molecular mechanism that is genuinely active in embryogenesis, but also recruitable for regenerative processes.

One might argue that the Spemann-Mangold organizer has its main function in activating Bmp/Chordin signaling for patterning the dorsal-ventral axis (De Robertis and Sasai, 1996). In cnidarians, Bmp/Chordin signaling is also active, primarily in the patterning of the directive axis (Kraus et al., 2016; Leclere and Rentzsch, 2014; Rentzsch et al., 2006; Rentzsch et al., 2007; Sinigaglia et al., 2013). In *Nematostella*, it was shown that the formation of this second axis is sensitive to an initial Wnt signal, but once established, the directive axis becomes Wnt- independent (Kraus et al., 2016). In vertebrates, Bmp/Chordin signaling of the organizer acts together with Brachyury in the marginal zone downstream of Wnt signaling (De Robertis, 2009; Hoppler et al., 1996; Meinhardt, 2006; Niehrs, 2004). Despite these similarities, the fate of the Bmp-driven second body axis is different in *Nematostella*. In all bilaterian animals, Hox gene-mediated patterning of the anterior-posterior axis is Wnt-mediated, whereas in *Nematostella*, it is Bmp-mediated. Not all cnidarians exhibit this Bmp-mediated directive axis. In *Hydra,* Bmp signaling acts along the oral-aboral Wnt axis (Holstein, 2022; Kirillova et al., 2018; Rentzsch and Holstein, 2018; Technau and Genikhovich, 2018).

A summary of how a cnidarian-like blastoporal organizer evolved into the bilaterian organizer was presented by Hans Meinhardt (Meinhardt, 2012) (Fig. 5d). Compelling evidence suggests that a Wnt/β-catenin-driven axial organizer served as the starting point in animal evolution, it predating the cnidarian-bilaterian split over 600 million years (Holstein, 2022; Holzem et al., 2024; Technau and Genikhovich, 2018). This organizer likely played a crucial role in a gastrula-like ancestor, controlling the development of an organism with mouth and blind-gut. The gastrula was initially postulated by Haeckel as the ancestral form of metazoans (Haeckel, 1874). Speculation arises that such an organism resembles the larval forms (planula) of modern cnidarians, which, in their late gastrula stage, possess the ability to hunt and capture food (Maegele et al., 2023).

The *Hydra* organizer discovered by Ethel Browne in Morgan's laboratory is thus likely closely related to the amphibian organizer uncovered by Hilde Mangold with Spemann. The blastoporal organizer was probably present in the common ancestor of cnidarians and bilaterians, serving as a springboard in the evolution of higher complexity in the Bilateria.

CRediT authorship contribution statement

Thomas W. Holstein: Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

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