"On the Induction of Embryonic Primordia by Implantation of Organizers from Different Species" (1924), Hilde Mangold's Dissertation [1]

By: Kearl, Megan MacCord, Kate Keywords: Organizers [2] Anatomy [3] Newts [4] Hilde Mangold (1898-1924) [5] Spemann-Mangold Organizer [6]

Hilde Pröscholdt Mangold was a doctoral student at the Zoological Institute at the University of Freiburg [8] in Freiburg, Germany, from 1920 to 1923. Mangold conducted research for her dissertation ?On the Induction of Embryonic Primordia by Implantation of Organizers from Different Species? (?Über Induktion von Embryonanlagen durch Implantation artfremder Organisatoren?), with the guidance of Hans Spemann [9], a professor of zoology at the University of Freiburg [8]. The dissertation was the culmination of five experiments on three species of newt embryos of the genus *Triton* (presently *Triturus* [10]), performed during the summers of 1921 and 1922, experiments that confirmed Spemann?s organizer [11] concept. Spemann and Mangold published the dissertation in a 1924 edition of *Roux?s Archives for Microscopic Anatomy and Developmental Mechanics* (*Roux?s Archiv für Mikroskopische Anatomie und Entwicklungsmechanik* [12]).

Mangold's experiments arose from issues raised in Spemann's 1918 article ?On the Determination of the First Organ Systems of the Amphibian Embryo? (?Über die Determination der ersten Organanlagen des Amphibienembryo I-IV?). In this 1918 article, Spemann found that by transplanting a piece of the blastopore [13] lip of a newt embryo into the embryo of a second newt, a second nervous system structure (a neural tube [14]) formed in the host. Spemann?s results suggested that the blastopore [13] lip acquired its fate before adjacent areas, and could then exert its influence on the development of surrounding tissues. This result became the basis of the organizer [11] concept; that is, the idea that certain regions of the embryo become specified before others, and that these specified regions influence the development of surrounding tissues. While Spemann?s 1918 article hinted at the role of the blastopore [13] lip as an organization center [15], he could not discern which part of the secondary neural tube [14] derived from the implant, and which part derived from the host.

In 1920, Mangold entered Spemann?s laboratory to conduct her doctoral research. After a failed series of attempts to recreate Abraham Trembley?s experiments in which a Hydra [16] is turned inside-out, Spemann assigned Mangold the problem of transplanting the blastopore [13] lip between species. Using mainly two species of newt, the crested newt [17], *Triton cristatus* and the smooth newt [18], *Triton taeniatus*, Mangold proceeded where Spemann?s 1918 article left off; by tracking the formation of neural structures through the transplantation of the blastopore [13] lip between embryos.

In the spring of 1921, Mangold began her experimental work by excising a section of the upper lip of the blastopore [13] from a *cristatus* embryo and implanting it into undifferentiated tissue in the *taeniatus* embryo. The natural cell pigmentation differences between the two

species allowed Mangold to easily differentiate the implanted and transparent *cristatus* dorsal lip tissue from the colored *taeniatus* cells. These pigmentation differences lasted throughout the course of development, enabling Mangold to observe the contributions that the transplants made to the growth of secondary neural structures.

Mangold allowed the host *taeniatus* embryo to develop to the point where both of the neural tubes had closed. After halting the embryo's development at this stage, Mangold cut it into sections as close to perpendicular to the neural tubes as possible so that she could further investigate the cell arrangements surrounding these structures. When Mangold looked at the cross sections, she saw that the overwhelming mass of the secondary neural tube [14] was made of the host *taeniatus* cells. Despite the majority of *taeniatus* cells, intercalated within a section of the neural tube [14], and underlying its length, there was a narrow mass of unpigmented cells from the *cristatus* transplant. The *cristatus* cells had folded inside of the embryo, through a process called invagination, and had resisted the influences of the surrounding *taeniatus* cells to develop as they would have in their original *cristatus* embryo. To Mangold, these results indicated that the *cristatus* dorsal blastopore [13] lip induced the surrounding host *taeniatus* tissue to form the secondary neural tube [14].

In the spring following her first experiment, Mangold performed four more experiments which further investigated the organizing power of the dorsal blastopore [13] lip. In her first experiment in 1922, Mangold excised a piece of upper blastopore [13] lip from a *cristatus* embryo at an early stage of gastrulation [19], and she implanted it into the midline of a *taeniatus* gastrula [20] of the same stage. In contrast to her first experiment, the implanted *cristatus* organizer [11] formed a unified mass of cells, not separated by a strip of mesoderm [21], as in the first experiment. This unified *cristatus* cell mass formed the entire precursor to the central nervous system [22], called the notochord [23], and again showed evidence of inducing the development of surrounding tissue. This experiment, as well as the 1921 experiment, confirmed the inductive power of the dorsal lip of the blastopore [13], but it failed to indicate whether or not the implant could form masses of tissue on either side of the neural tube [14] that become the dermis, skeletal muscle, and vertebrae, called somites [24], and it failed to indicate whether or not it could induce them to form in host mesoderm [21].

In the second experiment of 1922, Mangold exchanged materials in the same manner as in her previous experiments, but this time between advanced-stage, rather than early-stage, gastrulae. After allowing the embryos to develop for nearly 80 hours following transplantation, Mangold saw that the implanted organizer [11] participated in the formation of somites [24] surrounding the secondary neural tube [14] of the host embryo. Despite Mangold?s finding, the role of the organizer [11] in somite formation was still unclear because some of the somites [24] in the *taeniatus* embryo contained both clear and pigmented cells, indicating that both the host and implanted blastopore [13] lip helped form somites [24].

Hypothesizing that the mixing of cells within the somites [24] was due to the proximity of the *cristatus* implant to the host?s blastopore [13], in her next experiment, Mangold sought to correct for this possibility by placing the implant opposite the host?s organizer [11]. Mangold also chose to use a different species of newt, the Alpine newt [25], *Triton alpestris*, for this experiment, because its cells were even more darkly pigmented than those of *taeniatus*. Following the implantation [26] of the organizer [11] from an early gastrula [20]-stage *cristatus* into a blastula [27]-stage *alpestris*, Mangold received definitive results that the organizer [11] induced the surrounding cells of the host to develop into neural tube [14] and somites [24].

In her final experiment, Mangold repeated an earlier procedure wherein she transplanted a late-gastrula [20] stage *cristatus* organizer [11] into a *taeniatus* embryo of the same stage. This time, Mangold allowed the host embryo to develop for greater than 120 hours following transplantation before fixing and sectioning her sample. The longer timeline showed that Mangold?s implantation [26] of a second organizer [11] allowed for the development of a secondary embryo, with its own neural tube [14], notochord [23], and somites [24], but connected to its host at the trunk and sharing an intestine. The secondary embryo formed from cells of both the host and the implanted organizer [11].

Over the course of her dissertation research, Mangold transplanted the upper blastopore [13] lip 259 times, of which 73 embryos survived, and 28 of those embryos developed recognizable body features like a notochord [23] or most of a second body. The low success rate that Mangold achieved was not unordinary; the transplantation process made the embryos vulnerable to environmental factors like germs. Her experiments confirmed Spemann?s organizer [11] hypothesis, and demonstrated the extent to which the dorsal lip of the blastopore [13], now known as the Spemann organizer [11], can induce the formation of neural structures from its surrounding tissues.

According to a colleague of Mangold, Viktor Hamburger [28], Mangold was displeased when Spemann added his name to her dissertation, and especially at his insistence that his name precede hers. Her male laboratory peers, like Hamburger and Johannes Holtfreter [29], did not receive such treatment. In 1935, Spemann received the Nobel Prize for Physiology or Medicine for the discovery of the organizer [11] concept based in large part on Mangold's dissertation experiments. Mangold was not included on the award. Controversy has arisen because of Mangold?s exclusion from the Nobel Prize; however, the award is not given posthumously. Mangold died in a fire in 1924, around the time when the organizer [11] paper appeared in print.

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Subject

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