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Hans Spemann (1869-1941) and the Freiburg School of Embryology

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Introduction

In 1897, at the beginning of his scientific career, Hans Spemann (Fig. 1a,b) entered a field of research which was not only new and modern but which was also not well accepted by German biologists persisting in traditional styles of scientific thought. At the end of his life he was one of the most renowned zoologists world-wide (Leclerq and Dagnèlie, 1966) and *Entwicklungsmechanik* was established as an important experimental and causal-analytic working discipline in biology. In 1935 Spemann received the Nobel Prize for Medicine or Physiology as the first – and up till a few months ago only – embryologist. The prize-winning discovery, the so-called *organizer effect,* was the dominant topic in embryological research during the 1930s and, despite decades of subsequent disregard, in our days is experiencing a true renaissance.

Spemann's outstanding merits were his experimental and conceptual contributions to the biological discipline *Entwicklungsmechanik* (or *Entwicklungsphysiologie*, the term he preferred). His results helped to abandon the Roux-Driesch-controversy from the end of the 19th century and illuminated the fundamental but enigmatic mechanism of embryonic induction. The discovery of the organizer effect in Spemann's laboratory and the search for its physico-chemical foundations initiated the biochemical embryology of the 1930s and 1940s. On the basis of his experimental work, Spemann instructed and inspired a large group of younger scientists, among them Hilde Mangold, Otto Mangold, Johannes Holtfreter, Viktor Hamburger, Hermann Bautzmann, Else Wehmeier, Oskar Schotté, Eckhard Rotmann and Salome Gluecksoh(-Waelsch). Collectively they might be called the Freiburg school of experimental embryology which flourished especially during the 1920s.

The following paper will survey Spemann's main research topics and the fate of his school from the origins until its decline beginning in the 1930s. Also the question will be discussed why this scientific tradition was disrupted thereafter.

Spemann's scientific education in Heidelberg and Würzburg (1891-1898)

On scanning Spemann's curriculum vitae one will find some well-known scientists as his teachers. In Heidelberg he attended the lectures of the famous anatomist Carl Gegenbaur (1826-1903) and of the physiologist and cell biologist Otto Bütschli (1848-1920). In Würzburg Spemann was a student of Theodor Boveri, the co-founder of the chromosome theory of inheritance and famous cytological embryologist. The influential plant physiologist Julius Sachs (1822-1897) and the first Nobel Prize winner in physics, Conrad Wilhelm Röntgen (1845-1923), were also his teachers.

There is no question that among these teachers Theodor Boveri had the deepest intellectual influence on Spemann. Under his supervision Spemann prepared in 1894/95 his doctoral dissertation, a cell lineage study in the nematode *Strongylus paradoxus* (Spemann, 1895) for which he received the exceptional predicate 'summa cum laude'. For his *Habilitation* (the formal qualification for a professorship) Spemann explored the

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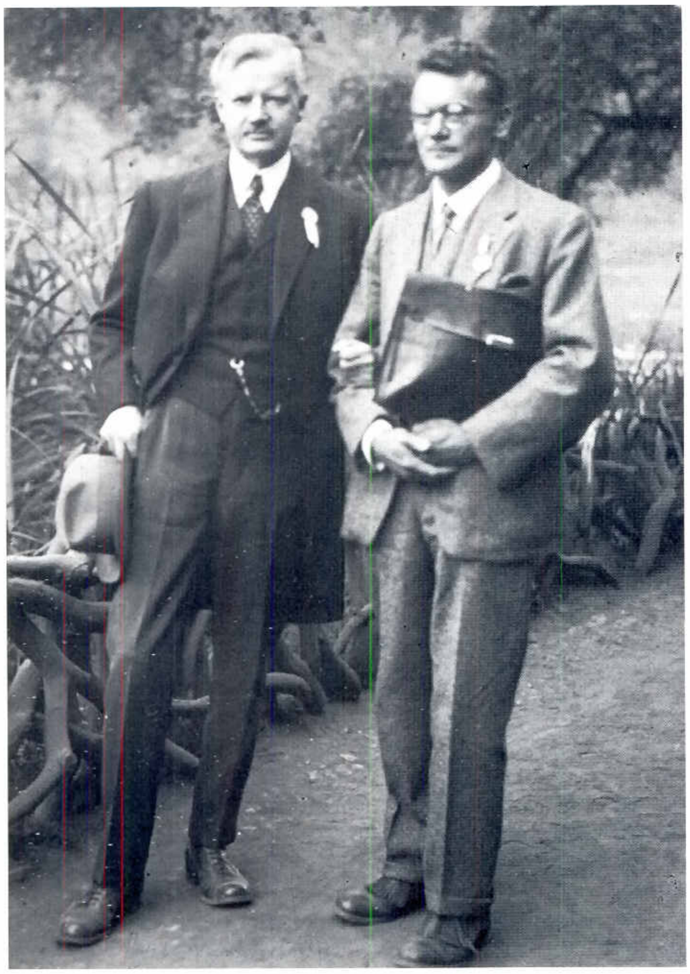


KUNGL. KAROLINSKA
MEDIKO-KIRURGISKA
INSTITUTET
VILKET ENLIGT TESTAMENTE, SOM
DEN 27 NOVEMBER 1895 UPPRÄTTATS AV
ALFRED NOBEL
ÄGER ATT MED

NOBELPRIS
BELÖNA DEN VIKTIGASTE UPPTÄCKT
VARMED DE FYSIOLOGISKA OCH
MEDICINSKA VETENSKAPERNA UNDER
SENASTE TIDEN RIKTATS, HAR DENNA
DAG BESLUTIT ATT TILLERKÄNNA
DET ÅR 1935 UTGÅENDE PRISET ÅT
HANS SPEMANN
FÖR HANS UPPTÄCKT AV ORGANISATOR-
EFFEKTEN UNDER DEN EMBRYONALA
UTVECKLINGEN.
STOCKHOLM DEN 24 OKTOBER 1935.

Fig. 1. (left) Hans Spemann and Karl v. Frisch, *zoologist and co-founder of modern ethology; Nobel prize winner in 1973 (1928; photographs courtesy of Dr. Brita Resch).* **(b) (right)** *Hans Spemann's Nobel title.*

embryonic development of the amphibian middle ear in a comparative analysis (Spemann, 1898).

Even before finishing this study, Spemann began in 1897 with experimental work in the field of *Entwicklungsmechanik*. That he did not share Boveri's special interests in cytological topics apparently was an act of intellectual emancipation from his adviser who had meanwhile grown his close friend.

There were several reasons for Spemann's decision to work experimentally on embryological problems:

The field of *Entwicklungsmechanik* confronted him with challenging practical and theoretical problems more than other disciplines did. In view of his extraordinary technical skills and broad philosophical interests this was a perfect combination.

The intellectual influence of scientists like August Weismann (1892), Gustav Wolff (1895), and August Pauly gave him the motivation and stimulus to focus on ontogenetical topics. But it is necessary to emphasize that - contrary to the opinion of some historians of science - Spemann gained intellectual distance to the psycho-lamarckistic position of his former friend August Pauly soon after beginning with his own scientific research.

There was also a pragmatic aspect in Spemann's option. At that time, experimental embryology was a young and modern discipline, which meant that this approach was little explored and therefore spectacular results could be hoped for.

Constriction experiments (1897-1905)

Spemann set out on his own research without a specific scientific concept in his mind. Rather he repeated experiments previously performed by O. Hertwig, H. Endres, and A. Herlitzka to test the ideas of Weismann and Roux. His technique was relatively simple. He used a hair loop to constrict eggs of the newt *Triturus vulgaris* (nomenclature at the beginning of the 20th century, Triton *taeniatus*), the hair (of which a curl persists in his files to this day) being taken from his blonde baby daughter Margerete (Fig. 2). Spemann varied three parameters: degree, plane, and stage of constriction.

Constricting two-cell-stages along the first cleavage furrow he obtained, in a minor fraction of cases, the malformation he called *Duplicitas anterior*: two heads merging posteriorly in a single body (Fig. 3a,b,c). The posterior limit of the duplication correlated positively with the degree of constriction. When Spemann separated the two blastomeres (or rather their descendants) completely, they sometimes developed into a pair of twins.

Duplicitas anterior and twins would only result when the constriction plane was congruent with the future median plane of the embryo's body (Spemann, 1903). In the other cases only one blastomere was able to produce a normal embryo while the descendants of the other were failing to form dorso-axial structures although comprising all three germ layers. Spemann called this relatively undifferentiated and unorganized ventral structure *Bauchstück* (belly piece) and ascribed its origins to frontal constriction (Spemann, 1902; fig. 4). The interpretation and deeper analysis of both these results contradicted Wilhelm Roux's (1850-1924) fundamental concepts, namely that of *self differentiation* (Roux, 1893), which should have lead to half embryos at best, and at the same time refuted Weismann's speculations about the germ plasm and unequal nuclear divisions (Weismann, 1892). On the other hand the *Bauchstück* showed that the amphibian egg was not necessarily the *harmonious equipotential system* envisioned by Hans Driesch (1867-1941).

As the *Bauchstück* did not produce any harmonious dorso-axial structures, its progenitor blastomere must have lacked a dorsalizing factor present in its sister blastomere. As documented by the twin embryos, the dorsalizing factor could not be ascribed to the nucleus but rather must be part of the protoplasm (Spemann, 1901).

Varying the stage of development at which the constriction was performed, Spemann found that the regulative capacity of the embryo decreased during gastrulation and neurulation. This important aspect he took up ten years later when, by transplantation experiments, he tested the fates of prospective epidermal and neural cells in atypical surroundings.

Lens induction (1900-1912)

Quite in contrast to his constriction experiments, Spemann started the analysis of lens development with a concrete question in mind which he tried to answer by different technical means. At that time no experimental data were available as yet which could provide a firm basis for Roux's concept of *dependent differentiation* during ontogenesis. Spemann wanted to shed light on this by analyzing the development of the amphibian lens with the techniques of extirpation and transplantation.

The first result obtained seemed to be clear-cut. After extirpation of the optic vesicle of *Rana fusca,* Spemann was not able to detect any lens vesicle (Spemann, 1901b; Fig. 5). Accordingly, lens development seemed strictly dependent on an inductive stimulus rooted in the eye cup. But soon afterwards, the Czech embryologist Emmanuel Mencl described a well developed lens in a trout embryo (*Salmo salar*) lacking the respective optic vesicle (Mencl, 1903). He called this phenomenon *free lens development* – a special case of self differentiation which directly contradicted Spemann's claim for dependent differentiation. The American embryologist Helen D. King supported Mencl's observation with experimental results obtained in *Rana palustris* (King, 1905). Thus was opened the 'lens controversy', kind of a special descendant of the Roux-Driesch-debate some ten years earlier. It was to last until 1912 when Spemann published his final conclusions in a general resumee which confirmed the observations of both parties (Spemann, 1912).

Spemann initially failed to believe the results of Mencl and in particular of King because *Rana fusca* and *Rana palustris* are very closely related and therefore it seemed to be unlikely that they should differ so fundamentally in their morphogenetic mechanisms. But when he tried to support his own hypothesis with experimental data from *Rana esculenta* he found to his surprise that they supported the findings of Mencl and King (Fig. 6). During the protracted controversy it became more and more clear that both ways of lens formation, induction *and* free lens development, were realized as morphogenetic mechanisms in amphibians. Even more surprisingly, both mechanisms were found side by side in one and the same species (Spemann, 1912): when the optic vesicle of *Rana palustris* was transplanted under the presumptive belly epidermis it caused this to form a secondary lens vesicle, but the head epidermis of the same species would develop a lens in the absence of the optic vesicle. Spemann took this to reveal the principle of *double assurance*, a term borrowed from the engineering sciences.

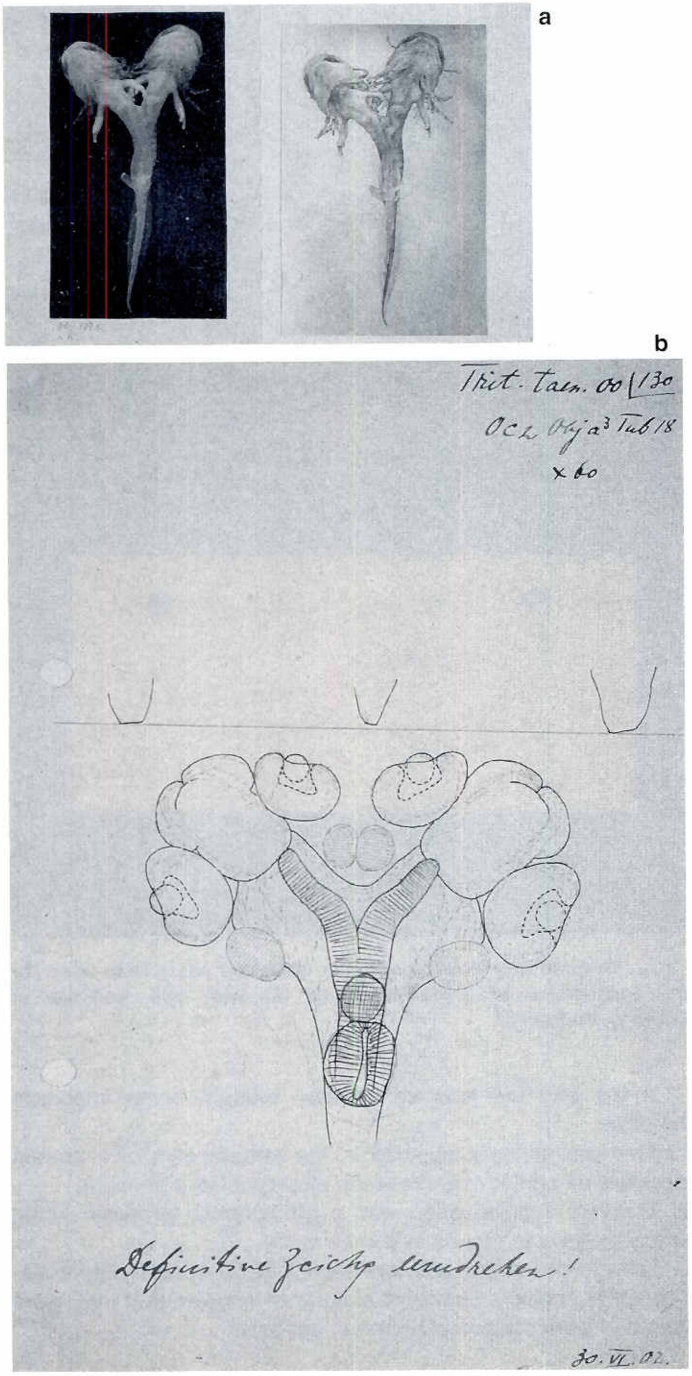
Fig. 2. Original hair from Spemann's daughter Margarete used for the constriction of amphibian eggs (around 1900; Institute of Zoology, Freiburg).

In the end the lens controversy brought some important insights:
1. The mechanisms involved in the ontogenesis of a certain structure can differ even between closely related species.
2. The fact that induction was a fundamental process during ontogenesis was proved in a case study.
3. The merger of self differentiation and dependent differentiation in the principle of double assurance showed that they were not alternative but complementary aspects.

Transplantation experiments (1915-1918): forerunners of the organizer experiments

In 1914 Spemann moved to Berlin-Dahlem, where he became the second director of the new *Kaiser-Wilhelm-Institut für Biologie* and the head of the department for *Entwicklungsmechanik*. It was a very fruitful scientific period in his life because experimental research was not handicapped there by any teaching obligations.

Spemann conceived new experiments which should answer the question during which stage the cells of the neuroectoderm become irreversibly determined to their later destiny. This ques-



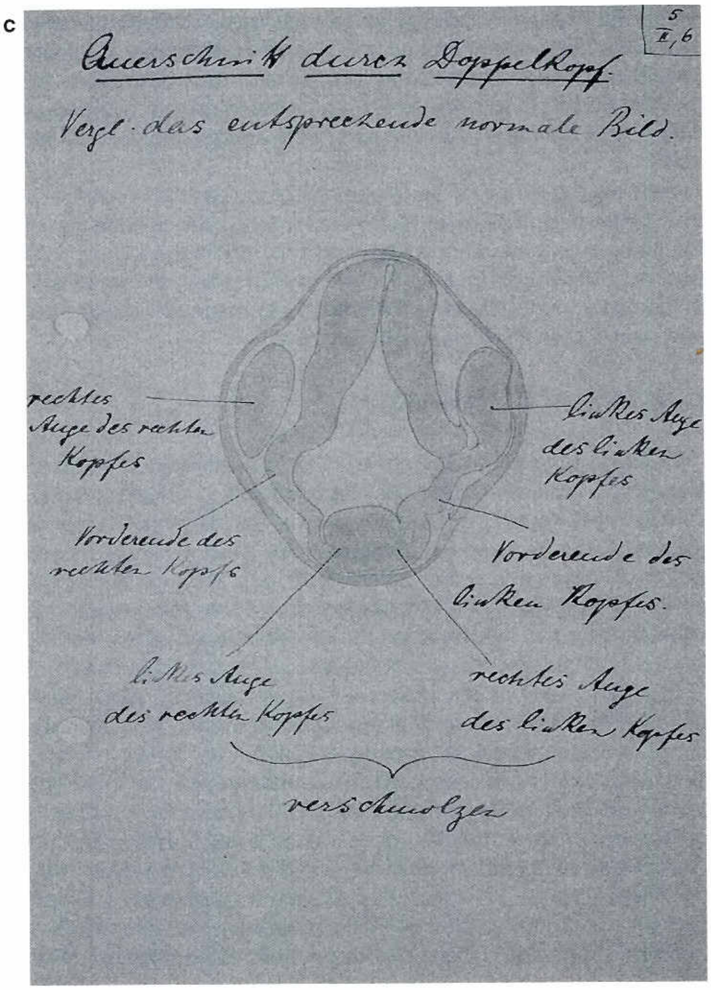


Fig. 3. Duplicitas anterior. *Double headed embryos of Triturus vulgaris developing after incomplete constriction along the first cleavage furrow.* **(a)** *Experiment Triton taeniatus (Triturus vulgaris)1900, 139c, photograph and drawing from ventral side (original by Hans Spemann in 1900);* **(b)** *experiment Triton taeniatus 1900, 130; drawing from the brain of a double headed embryo of Triturus vulgaris (original by Hans Spemann from June 30th 1902; right upper corner shows number of experiment and microscopical data);* **(c)** *experiment Triton taeniatus 1900, 5. Drawing of section through the anterior brain of Rana fusca showing a cyclopean defect; cross section through double head. [...] Right eye of the right head. Left eye of the left head. Anterior end of the right head. Anterior end of the left head. Left eye of the right head and right eye of the left head fused." (Original by Hans Spemann in 1901; upper right corner shows section number).*

tion arose because the constriction experiments had demonstrated that embryonic regulation capacity declined during gastrulation and therefore the presumptive neuroectoderm was probably determined at this stage. Now Spemann wanted to analyse this transition in more detail, using the technique of microsurgical transplantation.

In 1915 and 1916 Spemann performed homeoplastic transplantations of presumptive neuroectoderm into the host's prospective belly epidermis. As a first important result he realized that grafts from early gastrula stage embryos developed like their new surroundings in the host; in other words, the transplanted presumptive neuroectoderm had changed its prospective fate and become belly epidermis. Thus it had not yet been irreversibly determined. The same experiment but using grafts taken at the end of the gastrula stage showed a different result. Now the transplanted graft expressed the histological specificity of its original location, that is, a patch of neural tissue developed within the belly epidermis (Spemann, 1918). This finding seemed to support Spemann's assumption, based on the constriction experiments of fifteen years before, that the embryo's regulative capacity decreases during gastrulation and neurulation.

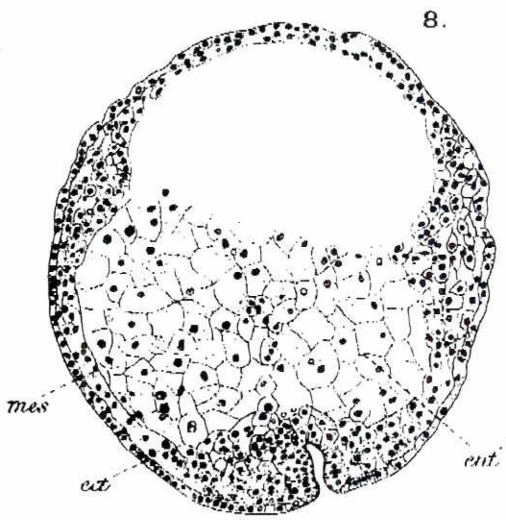


Fig. 4. Drawing of section through a *bauchstück* (belly piece) of *Rana fusca*. *The germ layers are identifiable but are not organized in any axial structure. mes, mesoderm; ect, ectoderm; ent, entoderm (Spemann, 1902).*

But there was one important exception, and this concerned dorsal blastopore lips transplanted at the early gastrula stage. After doing this experiment, Spemann despite the young donors found in the belly epidermis of the host some neural differentiation, accompanied internally by notochord structures. This was actually his first *organizer experiment,* dated April 20th 1916. But because donor and host came from the same species, all cells were identically pigmented and there was no possibility to decide whether the secondary axis was derived from host or graft material (Spemann, 1918). On the basis of Roux's mistaken fate map (see Sander, 1991), Spemann thought that the region of the upper blastopore lip consists of the prospective neuroectoderm, and hence he interpreted the secondary axial structures as the result of pure self differentiation. He thus fell into the very trap that prevented Warren H. Lewis (Lewis, 1907) from recognizing that frog dorsal lip may possess neural inducing capacity.

But in contrast to Lewis, Spemann noted the underlying notochord. At first he explained its origins in the frame of the then current paradigm: he assumed that the transplanted graft had included two layers of cells – the outer layer representing prospective neuroectoderm and the inner layer prospective chorda-mesoderm (Fig. 7). Consequently he concluded that the determination of neural fates has not only a temporal dimension but also is progressing in space. Beginning in the dorsal blastopore lip, the determination was to spread over the neuroectoderm towards the future head region. From this point of view Spemann designated the dorsal blastopore lip a *Differenzierungszentrum* (Spemann, 1918).

But soon after the publication of this concept Spemann realized that the dorsal blastopore lip was not a stationary structure but underwent involution during the gastrula stages. This made the presumed self-differentiation of the transplanted cells appear more and more unlikely. To check on this he decided to repeat the experiment, but this time using the differently pigmented embryos of two newt species – a technique (Spemann 1921) which he had developed in 1917. By this approach he hoped to identify the origins of the secondary axial structures. But owing to his move in 1919 to Freiburg i. Br. he was lacking for six years the time for working at the bench himself. Therefore in the spring of 1921 he delegated this cherished experiment, later called the *organizer experiment,* to his student Hilde Mangold née Pröscholdt (1898-1924; Fig. 8) for her doctoral dissertation.

During two breeding seasons, 1921 and 1922, Hilde Mangold transplanted about 470 grafts and in some 30 hosts obtained secondary axial structures, most of them fairly incomplete. The best secondary individuals clearly showed a chimeric composition. Thus it became obvious that the transplanted tissue of the dorsal blastopore lip acted as an *Organisator* integrating graft and host tissue into a composite secondary axial system (Fig. 9). This spectacular result, the *organizer effect,* was published in 1924 (Spemann and Mangold, 1924).

Hilde Mangold was not happy when Spemann put his name first, but Victor Hamburger (Hamburger, 1988) feels that

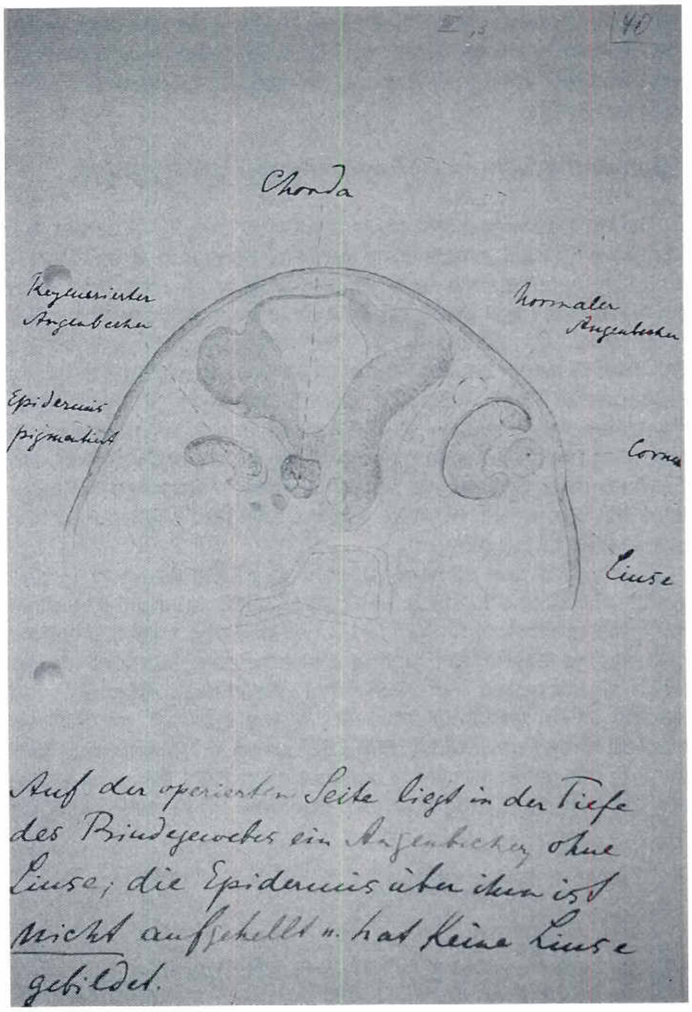


Fig. 5. Drawing of section through the brain of *Rana fusca*. *After extirpation the left optic cup regenerated without reaching the epidermal layer. Therefore the lens formation failed. Experiment Rana fusca 1901, 40; "Eye cup without lens in the depth of the operated side; the overlying epidermis failed to clear up and form a lens." (Original by Hans Spemann in 1901; section no. II, 3).*

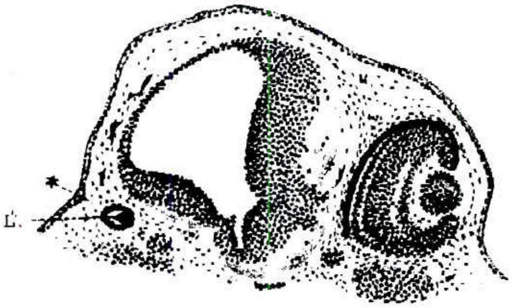


Fig. 6 Drawing of section through the brain of *Rana esculenta*. *Although the eye cup was extirpated a lens vesicle developed autonomously. L!, lens vesicle (Spemann, 1912).*

Spemann was justified in doing so. His point of view is supported not only by the fact that Spemann conceived both the problem and the techniques by which to approach it, but also by Spemann's diary notes. They show (Fäßler, unpublished result) that Spemann invested over 50 hours (and maybe close to 100 hours) in discussing, writing and pruning the manuscript for the joint publication.

Spemann's School of Experimental Embryology

During the second half of his academic career – a career that altogether lasted almost forty years – Spemann assembled a school of experimental embryology devoted to a common field of research: the exploration of embryonic induction and the organizer effect by microsurgery. The next paragraph will outline Spemann's closer circle of students and collaborators and briefly characterize their scientific contributions to *Entwicklungsmechanik*. Unnecessary to emphasize that it is impossible to name and appraise all members of his laboratory. After all, the *Festschrift* for Spemann's sixtieth birthday comprises contributions by 73 authors, of which the majority had worked with him at one time or the other.

Spemann's first doctoral student was Otto Mangold (1891-1962) who began to study with him in 1912, during Spemann's interlude at Rostock (1908-1914). After World War I, Mangold followed his teacher to Freiburg where he completed his dissertation and obtained – in 1921 – his *Habilitation*. Afterwards he worked as an assistant professor at the Institute. In 1921 he married Hilde Pröscholdt (1898-1924) who at that time was performing the experiments for her thesis. In 1924 the young couple moved to Berlin-Dahlem because Otto was elected Spemann's successor at the *Kaiser-Wilhelm-Institut*. In the same year Hilde Mangold died from a tragic accident. Otto Mangold stayed in Berlin for altogether about nine years and then moved in 1933 to the University of Erlangen in Bavaria where he held the chair for *Entwicklungsmechanik*. When Spemann retired in 1936 he supported the faculty's choice of Mangold as his successor. In 1937 Mangold returned to Freiburg and took over the chair for zoology which he lost eight years later for political reasons.

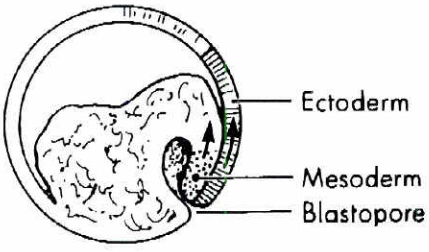


Fig. 7. Spemann's mistaken interpretation of the dorsal blastopore lip (Hamburger, 1988).

Fig. 8 Hilde Mangold, née Pröscholdt (1918). *Photograph courtesy of Prof. Klaus Sander.*

Otto Mangold was Spemann's successor not only in his professional positions at Dahlem and Freiburg but no doubt also in his scientific approach. In an early study he analysed the specificity of the germ layers. An important result was that the germ layers do not show a strict specificity during early embryonic stages (Mangold, 1923, 1925). For example he demonstrated (some time before the organizer effect became known!) that transplanted prospective epidermis still owns the potency to develop into mesodermal structures like somites or notochord. Together with his wife, he modified in 1923 the organizer experiment so that it should reveal the spatial limits of the organizer region. The results (H. Mangold, 1929) were published belatedly because of his Hilde's early death. At the Kaiser-Wilhelm-Institute Mangold conceived the so-called *Einsteckmethode*, pushing grafts into the blastocoel (see Fig. 7) instead of incorporating them into the epidermal layer (O. Mangold, 1929). This method was very important because it helped to decrease the rate of embryonic mortality and was easier to practise than the traditional technique of implantation.

In 1927 Mangold and Spemann discovered independently and in different experiments the so-called *homeogenetic induction*. They published this in a joint paper (Mangold and Spemann, 1927). The term means that transplanted prospective

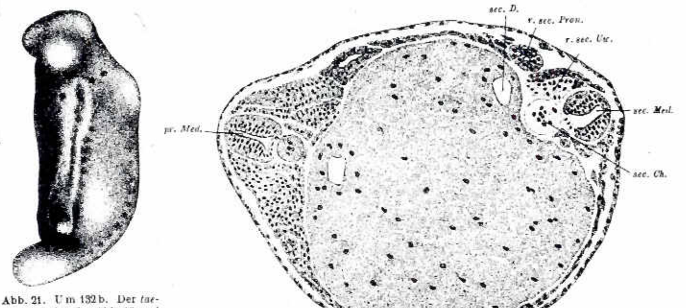


Abb. 21. Um 132b. Der *taeniatus*-Keim der Abb. 19 und 20, weiter entwickelt, von der linken Seite gesehen. Aufsicht auf die sekundäre Embryonalanlage mit Schwänzchen, Medullarrohr, Urwirbeln und Hörblasen. 20 ×.

Abb. 24. Um 132b. Querschnitt durch die Mitte des Keims (vgl. Abb. 21). Auf Abbildung links die primären, rechts die sekundären Achsenorgane. *r. sec. Pron.* rechter sekundärer Vornierengang. Implantat (hell) als Chorda und im rechten sekundären Urwirbel. 100 ×.

Fig. 9. The most famous organizer experiment *Triton 1922 Um 132b.* **(a)** *Drawing of the embryo showing the secondary neural tube in the left flank;* ***(b)*** *drawing of section through secondary embryo obtained in the organizer experiment labeled "Triton taniatus 1922, Um 132b" (Um, Urmund; blastopore). The axial structures of the chimeric secondary embryo are shown at the right (Spemann und Mangold, 1924). pr.Med., primary neural axis; sec.D., secondary gut; r.sec.Pron., right secondary pronephros; r.sec.Uw., right secondary somite; sec. Med., secondary neural axis; sec. Ch., secondary notochord.*

neural tissue can, in the absence of any inductive stimulus from the chorda-mesoderm, induce secondary neural structures in presumptive belly epidermis. This finding confirmed Spemann's earlier notion of a planar transmission of the inducing stimulus (Spemann, 1918). In a very influential study, Mangold (1933) detailed the regional specificity of inductions by the chorda-mesoderm. Spemann had discovered this specificity two years earlier when he coined the terms *head organizer* and *trunk organizer* (Spemann, 1931; Fig. 10).

After the dorsal blastopore lip was identified as the embryonic *organizer region* in 1921 there still existed not much knowledge about its spatial extent. It was Hermann Bautzmann, another doctoral candidate of Spemann, who demonstrated the *spatial extent* of the organizer region dorsal and lateral to the blastopore (Bautzmann, 1926; Fig. 11).

After exploring several aspects of the organizer effect, such as the orientation of the secondary embryonic system, the extent of the organizer region, and organizer effects in other taxa, the Spemann school focused on the *material basis* of the organizer effect. Probably the most innovative and productive student of the Spemann school was Johannes Holtfreter (1901-1992). His first and invaluable contribution was the recipe for the *Holtfreter solution* (Holtfreter, 1931), a physiological medium for amphibian embryos which decreased their exorbitant mortality and made experimental work much more effective. In 1932 Holtfreter together with Bautzmann, Wehmeier and Spemann was able to prove the inductive capacity of *devitalized organizers* (Bautzmann *et al.,* 1932). Since also the extraction of inducing substances was achieved, the *chemical nature* of the organizer effect became a widely accepted fact at the beginning of the 1930s, and this triggered a trend toward biochemical methods in embryology. Holtfreter and other authors published many papers on inducing substances – with the result that after some years of intensive research so many effective substances were known that a biochemical analysis of the organizer effect seemed beyond reach (Holtfreter, 1934; Rotmann, 1949). The biochemical work begun in the 1950s by Heinz and Hildegard Tiedemann (Tiedemann 1963) under Mangold's influence gave some promising leads, but amphibian developmental biology on the whole had to wait for the advent of molecular biology for a new and more promising approach to this problem.

The genetical approach to embryonic organization, so successful recently in *Drosophila* and *Caenorhabditis*, is beset with well-known handicaps in amphibians. However, it was not even attempted in Spemann's school, partly because Spemann himself felt no "affinity" for genetics. When Bruno Geinitz, Oskar E. Schotté and Eckhard Rotmann found that inducing stimuli can act across the borderline between urodeles and anurans, Spemann (1936) was satisfied with ascribing the species-specificity of the induced structures to the *Erbschatz* (inherited property) or *Potenzschatz* in general rather than to the genes in the reacting cells.

One of Spemann's favorite students was Viktor Hamburger (born in 1900). He began to study with Spemann in the spring of 1920, together with Hilde Pröscholdt (later Hilde Mangold) and Johannes Holtfreter (see the cover illustration of this issue). After completing his doctoral thesis in 1924 he moved to Munich but came back in 1928 taking up the position of assistant professor at the Zoological Institute. His research plans differed from Spemann's and mostly aimed at neural embryogenesis (Hamburger, 1928). After travelling to the USA to work under a Rockefeller fellowship in 1932, Hamburger (who comes from a Jewish family) saw no sense in returning to Germany after the Nazis had taken over. He stayed in the United States and there became the main founder and a leading exponent of neuroembryology.

The decline of the Freiburg School

After the 1930s the Freiburg school of embryology lost its world-wide leading position in organizer research. The causes for this trend were both internal and external:

The microsurgical techniques practised in Freiburg had reached their limits of usefulness and the available biochemical methods were not yet good enough for exploring the material basis of induction.

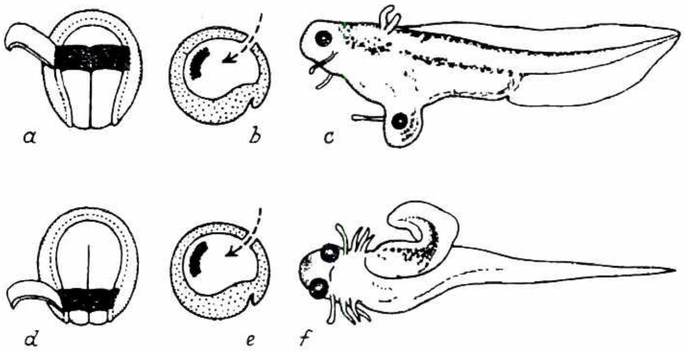


Fig. 10. Regional induction specificity of the archenteron roof, demonstrated by the *einsteck-method.* **(a-c)** *Transplantation of head-inducing mesoderm;* **(d-f)** *transplantation of trunk inducing mesoderm (Mangold, 1953).*

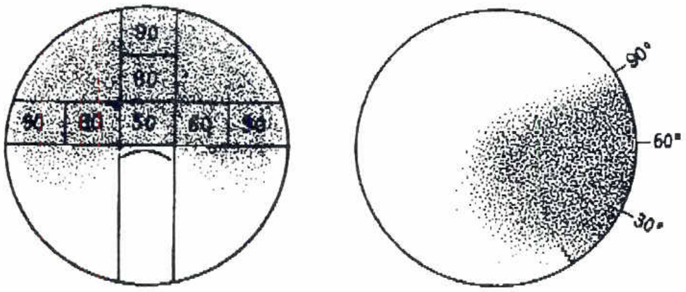


Fig. 11. The extent of the organizer region at the beginning of gastrulation *(Bautzmann, 1926).*

Spemann's favorite object, the Urodelan embryo, is not suited for a biochemical or genetical approach, nor was genetics in general advanced far enough in his time. The species used could not be bred all the year round, and mortality among operated embryos was high (the first sulfonamide drug had just been discovered in Germany but was not available yet).

The personal continuity of the Spemann school ended rather soon. During the 1930s several collaborators, notably Hamburger and Gluecksohn-(Waelsch) were forced into emigration by the political conditions in national socialist Germany; others, like Holtfreter and Schotté, although not in imminent danger, chose to remain abroad. They all continued in developmental biology but more or less changed their fields of research. Otto Mangold stayed in Germany and was installed by the government as the rector of the University of Freiburg in 1938. He resigned under protest in 1941 but his collaboration with the Nazis lead to his dismissal from the university in 1945. He continued working at a largely private research institute located at Heiligenberg near Lake Constance but his means for attracting collaborators were very restricted.

Finally, the outbreak of World War II, the total defeat of Germany in 1945, and the subsequent years of distress and isolation from the international scientific community handicapped – and largely paralyzed – scientific work and progress.

But one should emphasize that, in the complex network of factors that caused the decline of the Spemann school of embryology, the inherent limitations of the microsurgical approach were a major component.

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