

Morphogenesis, Seidel's legacy for developmental biology and challenge for molecular embryologists

HELMUT W. SAUER¹, FRITZ E. SCHWALM²
and KARL B. MORITZ³

¹Texas A & M University, College Station, Texas,

²Texas Woman's University, Denton, Texas, USA and

³LM University of Munich, Munich, Germany

Friedrich Seidel (1897-1992) studied chemistry, physics, biology, and philosophy in Tübingen, Hamburg, and Göttingen before he became the first student of Alfred Kühn. As we know from Kühn's masterly textbook 'Vorlesungen über Entwicklungsbiologie' (Springer 1965), Seidel must have been thoroughly exposed to the multitude of experimental systems and the full range of questions of the classical period. A visionary attempt to unify views of development, inheritance, evolution, and ecology had been presented in 'Das Keimplasma. Eine Theorie der Vererbung.' (1892) by August Weismann, the teacher of Kühn. Seidel's PhD thesis (1923) dealt with a classical theme, the segregation of germline and soma. He investigated the development of the reproductive organs and germ cells of the hemipteran insect *Pyrhocoris*. Seidel became an experimental embryologist, abruptly, after he heard a talk by Hans Spemann at the Meeting of the German Zoological Society (1921) on his transplantations with newt embryos. These experiments defined the enigmatic property of 'regulation', first discovered by Hans Driesch (1892), when isolated blastomeres of 2- and 4-cell sea urchin embryos 'regulated' into normal, just smaller pluteus larvae. This remarkable behavior was evidence for Driesch that the embryo is a 'harmonious equipotential system', inaccessible to analysis and controlled by a vital force. However, Theodor Boveri found, from the developmental restriction of blastomeres of the 8-cell stage and already of the one-celled embryo after cutting it into an animal and a vegetal half, that this system is not equipotent. Instead, the egg is anisotropic, and the vegetal half contains a 'privileged region' which organizes morphogenetic movements at the onset of gastrulation.

This was the topic that was further elucidated by Spemann's transplantation experiments. He found that an implant in an early gastrula-host developed conditionally. An implant from the late gastrula, however, developed autonomously, thereby indicating its determined state. An unanticipated result was obtained after transplanting the dorsal lip of the blastopore: not only did it develop autonomously earlier on, but it also changed the fate of the nearby host blastema to 'induce' a second neural plate and a complete second body axis, hence Spemann's organizer.

Together with Otto Mangold, Seidel traced the mysterious 'organizer' to the 2-cell stage in Spemann's laboratory at the Kaiser Wilhelm Institute (1924-25). They fused cross-wise pairs of embryos at the 2-cell stage and obtained either a single normal (giant) newt, or partial or complete twins, or even partial triplets and quadruplets. The extent of regulation appeared to depend on the ability of the cytoplasmic factor region to move, to fuse or to separate, and to signal across the membranes of blastomeres. Heteroplastic embryo fusions demonstrated that the organizing capacity is not species-specific. These experiments revealed embryos as dynamic systems. They are fully integrated in Spemann's brilliant account 'Embryonic Development and Induction' (Yale University Press, New Haven, 1938, pages 271-275). With hindsight we note that Mangold and Seidel detected organizing factors before the establishment of the Nieuwkoop center.

Seidel next held a position at the Zoological Institute at Königsberg where he was awarded *venia legendi* for Zoology and Comparative Anatomy (1926). In 1936 he moved to the University of Berlin and became full professor and Director of the

*Address for reprints: Department of Biology, Texas A&M University, 315 Biological Sciences Building West, College Station, TX 77843-3258, USA. FAX: 409.8452891. e-mail: SAUER@BIO.TAMU.EDU

Zoological Institute a year later. During this time, Seidel established himself as a highly original researcher. Over a period of ten productive years of painstaking experimentation and visionary interpretation he single-handedly established damselfly *Platycnemis* as the 'paradigm of insect development'. The transparency of the *Platycnemis* embryo offers the opportunity to probe for cytoplasmic 'factor-regions' without disturbing the proliferation of nuclei.

He discovered the 'Bildungszentrum' (formation center, activation center) near the posterior pole, and its activation by any isopotential cleavage-energid (a nucleus surrounded by a portion of cytoplasm, typical of the plasmodial phase of insect development). This activation results in a visible signalling event which, in turn activates the 'differentiation center'. To this major organizer region, he attributed two functional features. (1) Its 'physiological' quality is centered in the 'yolk-endoplasm-system', and it prepares the form (template) of the lateral germ rudiments, itself visible as an aggregate of still uncommitted cells. (2) Its 'morphological' quality is revealed as the 'initiation region' of differentiation. It becomes directly detectable in the process of morphogenesis, specifically the onset of embryonic segmentation, beginning with the prothorax.

More generally, he concluded from his comparative studies that the diversity among (insect) embryos does not represent a range from mosaic to regulative types of differentiation. It is instead an expression of earlier or later differentiation of embryonic regions. Spemann was aware of Seidel's extraordinary achievements when he recommended him to give a major address at the 1936 meeting of the German Zoological Society because of 'the uniqueness and originality of the choice of his experimental subject and the universal implications of his results.'

Seidel and Gerhard Krause, his first student who contributed the 'cleavage center' as a third factor region, defined a wide spectrum of insect egg-types. This work was extended later by Seidel in Marburg, and Krause in Würzburg. Regulation after experimental challenge provided speculations about mechanisms of pattern formation and morphogenesis in insects in general. These studies published in great detail by some 20 doctoral studies of Seidel alone, was definitively summarized by Seidel (1965) 'Das Eisystem der Insekten und die Dynamik seiner Aktivierung' (The egg system of insects and the dynamics of its activation). By that time Seidel had become the Nestor in insect development not only in Germany (see C. Counce Ref. in Schwalm 1988).

While supervising his students' research on insect embryos, Seidel initiated another set of highly original experiments on the mammalian embryo. These investigations began after the second world war at the MPI for Animal Breeding in Mariensee/Hannover. They were further pursued after Seidel became Director of the Zoological Institute at the Philipps University at Marburg. Rabbit embryos facilitated observation of germ disc morphogenesis. Seidel succeeded with *in vitro* culture of early embryonic stages. He manipulated these embryos and obtained full term development in foster mothers. He was the first to produce normal fertile rabbits from single blastomeres of 2- and 4-cell stages. This work was instrumental for embryo-cloning in mammals, stimulated much fundamental research into the uterine environment of the embryo and was of considerable impact

for progress in the field of human reproduction. Seidel concluded, from electronmicroscopical analysis of the egg, and a statistical analysis of the success rate of blastomeres resulting in normal embryos, that the rabbit egg must be anisotropic. As shown for the newt and insect egg, he proposed that an organizing region must also be operative in the mammalian embryo. His concept was met with skepticism, but he remained unconvinced that the more recent results with mouse embryos demonstrated conclusively their non-polar organization at earliest stages.

Seidel's encyclopedic knowledge about morphology and developmental histories led him to re-evaluate the significance of the 'canonical' stages of ontogenesis. To him the central event of the embryo's life occurs during the period in which the basic body plan, 'Körpergrundgestalt' in his term, becomes apparent. It is not gastrulation. These 'typical' body patterns reveal for the first time all the pattern elements characteristic of the respective animal phyla. With this view Seidel follows the tradition of Carl Ernst von Baer's comparative developmental histories. Since 1967, as professor emeritus, Seidel devoted his major efforts to win experts to contribute to a multi-volume 'Handbuch der Morphogenese'. In the first volume Seidel (1978) gives a full account of the implications of his 'Körpergrundgestalten' to development and evolution. Some evolutionary biologists were not amused. The enormous endeavor of the Handbook remained unfulfilled. Seidel hoped someone would continue with an English version of his Masterplan. One of the volumes was dedicated to 'Insect Morphogenesis' and has since been published separately. In the preface to this volume (Schwalm 1988, quoted with permission) Seidel, at the age of 90, gives a wise account of his ideas of morphogenesis and insect development. This lucid insight after a full life may give posterity a rare glimpse into the mind of a scientist with a broad range of experiences who was at a center of embryological research for the major part of the 20th century:

"The term 'development' has always had a magic ring for scholars who have been inspired by varying endeavours. It has not only fascinated natural scientists. Philologists and sociologists, as well as biologists, are concerned with comparable problems and similar views. In the context of insect development one can ask whether anything has changed since the end of the previous century that would necessitate a reorientation of previously accepted methods in the study of developmental biology.

A glimpse at the history of our science reveals the following: the study of development at the beginning of the 19th century, as represented by Carl Ernst von Baer, meant to describe biological form, and to analyze and compare the abundant variety of observations in order to detect unifying principles. Thus the study of 'pure morphology' was based on a clear, translucent and idealistic methodology. This method of developmental studies was perturbed significantly when Charles Darwin and Jean Baptiste de Lamarck introduced the theory of descent of animals into biological studies. Never before had a single theory revolutionized the field from which it sprang as much as the new theory of descent. Today evolutionary theory has a deep impact on the traditional study of biology. Entirely new perspectives opened up for the study of present conditions. It became necessary to accommodate new ideas which included life cycles, successions of generations, and the history of the earth.

The impact on developmental studies was more than quantitative. As implied above, the quantitative expansion of natural history necessitated qualitative structural changes. Additional disciplines, such as geology, paleontology and biogeography, became indispensable and immediately claimed a certain autonomy. They generated results which had to be integrated into biological contexts and which may demand a rearranging of taxonomic systems of present forms, or which may even overthrow phylogenetic constructs that had previously been firmly accepted.

The phylogenetic context of anatomical parts and in the functional aspects of the morphology of organisms has an even graver impact on current biology. We see the emergence of an 'evolutionary morphology' replacing the 'pure morphology', and the transition often passes unnoticed. This change in the content becomes apparent in scientific definitions: their practical application may undergo a complete transformation. Animal morphologies no longer represent the 'idea' of the basic body plan but they are considered to be its realization. Homologies are henceforth not only found in similar morphological positions, but presumed to share a common phylogenetic origin. Thus it has become established that anatomical parts or a morphological pattern are to be considered homologous if they can be derived from a common anlage in the basic body pattern, the 'Körpergrundgestalt', before organisms underwent their phylogenetic diversification. Homologous organs are concrete 'heirlooms' of a common ancestor. Biological systems have been transformed into phylogenetic trees. Of course, one cannot criticize the resulting evolutionary aspects of morphology as long as they are based on testable assumptions.

However, difficulties have existed and still have not been overcome ever since Ernst Haeckel integrated phylogenetic and ontogenetic observations into his 'biogenetic law'. This law imposes certain constraints for biological development because ontogeny supposedly represented a rapid recapitulation of phylogeny. Haeckel's central example is the gastrula stage which he initially discovered. The cup-shaped gastrula stage of the calcareous sponges can be observed in many metazoan embryos. According to the biogenetic law it should be derived from an ancestral organism, the 'gastreae', representing a phase in evolution that is being recapitulated by all embryological gastrulae. Two assumptions made by this theory are debatable and demonstrate the uncertain foundation of the entire 'law': the existence of such a prototype, an adult-stage gastrula, can only be deduced, hypothetically, from phylogenetically linked successions of organisms. Exact proof has not been provided by biological or paleontological observation, only generalized assumptions remain. The ancestral organism (Stammtypus), the 'gastreae', has not been identified either as a solitary marine organism or as a member of any taxon of the Animalia. Therefore, the monophyletic origin of the entire kingdom, as postulated by Ernst Haeckel, stands on shaky ground. On the other hand, examples based on ontogenetic observations, which are supposed to support the monophyletic origin of the kingdom, can only be found in a few acceptable cases. Only in few instances, mainly after total cleavage, does a typical gastrulation process lead to the formation of germ layers.

It is fascinating to observe which daring constructions and which contorted arguments some authors have employed in

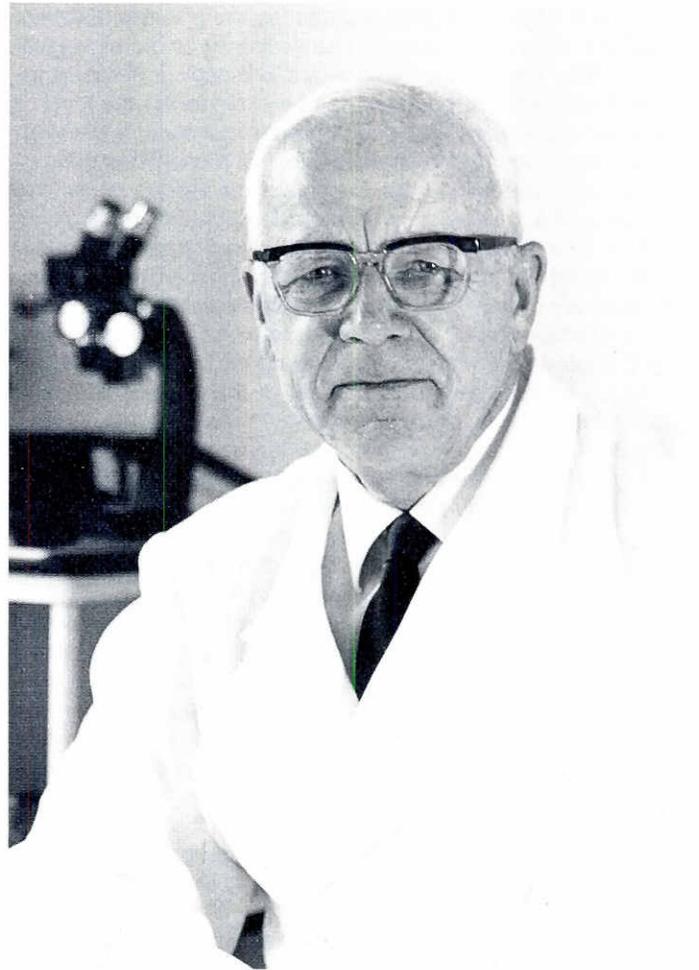


Fig. 1. Friedrich Seidel (1897-1992).

order to deduce the anticipated and highly desirable gastrula stage. It should just be recounted which events are construed to represent gastrulation: polar or multipolar immigration of cells, or delamination; the in-folding of the margin of a germinal rudiment, or the formation of a primitive groove in its centre. Finally it became acceptable to consider just any process by which cells of a germinal rudiment segregate to form an internal or external, or an upper and lower layer of cells to represent a bona fide gastrulation. One simply hesitated to abandon the concept of gastrulation because the reference to the hypothetical common ancestor 'gastreae' provided a common element for the classification of all Metazoa.

These untenable constraints require a rational reorganization and a liberation from historical ballast. We need instead to rely on other disciplines, particularly the branch of developmental physiology that focuses on the driving forces of morphogenesis (causal morphology) which relies on the methodology used in morphological research.

Studies in developmental physiology are characterized by the fact that they can only be performed on living organisms in experiments with living structures. The organism consists of a system in which diverse anatomical parts are co-ordinated logi-

cally and in which analytical approaches are possible. External shape and internal structure can be examined by morphological means. They can be elucidated with microscopic and submicroscopic investigations, and they can be extended to the level of molecular interactions. But only a proper approach of developmental physiology based on morphological foundations will provide an understanding of the function of the various parts. The findings on the physiological interactions of organismic systems must be added to the observations on morphological structure. The living system that constitutes an organism can only be characterized when both types of research are combined.

A systems analysis of that kind has been attempted with insect eggs and embryos in various ways. For example, an investigator may apply local defects in the surface layers of eggs of damselflies; these eggs are 800 μm long and 200 μm wide. Such defects can be precisely localized by using microcautery, narrow beams of ultraviolet light or X-rays. Reactions of the entire system may result in deletions in the body pattern, or in regulative correction of defects, and thus reveal the ability of the system to cope with such assaults. Small defects have revealed significant differences regarding the capacity of different egg regions to control the movement of portions of the egg content or in their ability to enhance or suppress specific developmental processes. More incisive interference with the system, such as a splitting of the egg content at the anterior or posterior poles, can lead to duplications or threefold repetition of parts of the resulting organism. Artificial blockade of the longitudinal continuity of the egg can cause formation of dwarfs. Each one of these modifications will motivate the investigator to seek explanations for the alteration of the developmental pathways in order to reveal causes and effects of normal developmental events.

The study of 'developmental centres', which initiate distinct developmental processes in insect embryos, is particularly revealing. Injury to these cytoplasmic centres or their removal from the egg lead to irreparable damage. Three such centres have been identified and have been analyzed in detail in some insect embryos: the cleavage centre, the formation centre and the differentiation centre.

The cleavage centre [Krause, 1938] consists of a cytoplasmic egg region in which nuclear fusion of the pronuclei occurs and where the first and subsequent nuclear divisions are initiated. The spherical accumulation of endoplasm in the cleavage centre is connected to the network of endoplasm by pseudopodial extensions which reach into the periplasm at the egg surface. Dynamic redistributions of endoplasm throughout the entire egg are thus facilitated by the egg architecture.

The entire system of 'yolk-endoplasm' begins to move after fertilization. Oscillatory movements of various egg regions can be deduced from transient displacements of yolk platelets. They originate at the site of fertilization and eventually reach the two poles of the egg. These movements seem to loosen up the egg system and prepare it for successive developmental processes. Among these processes is the distribution of energids (cleavage nuclei surrounded by a cloud of cytoplasm) during internal and superficial cleavage stages. The endoplasm that surrounds the zygote nucleus and subsequently all new energids develops a special system of contractile mechanisms (radial system; Hujer, 1975) which interconnects all cleavage nuclei and pro-

vides the motive force and the direction of their distribution throughout the egg.

The yolk-endoplasmic-system appears to be prepared for the accommodation and distribution of energids in yet another way, revealed by the dynamics of pseudocleavage, studied in *Gryllus* eggs which lack a nucleus [Mahr, 1960]. At the stage that corresponds to synchronous distribution of nuclei in the normal embryo, the network of endoplasm accumulates in cytoplasmic islands, eventually resembling the 512-nuclei stage and extending over the entire egg volume. However, in this instance, only cytoplasm from the endoplasmic network accumulates. Factors derived from the cleavage centre and the stimulus to move energids to the surface of the egg system are missing.

This stimulus may be provided by the second developmental centre, a local cytoplasmic region at the posterior pole named formation centre (Bildungszentrum, *Platycnemis*, Seidel 1929). When this formation centre (the posterior 10% of the egg) is removed or destroyed by cauterization the egg loses its ability to produce a germinal rudiment. Only extraembryonic components can be formed. The activation of this centre coincides with the end of synchronous cleavage; it is accomplished by one of the isopotential energids, namely, the first one to enter the posterior egg region. Microcinematographic time-lapse photography shows that this energid becomes enlarged by excessive amounts of cytoplasm. This event may provide the morphological-cytological basis for the formation of the embryo which is the function of this centre.

The activation of the formation centre by a descendant of the zygote nucleus in the cleavage centre has cytological and physiological consequences; asynchronous nuclear divisions, lengthening of the cell cycle, formation of a cellular blastema and dissolution of yolk platelets. The consistency of the entire yolk-endoplasmic-system changes, progressing from the posterior toward the anterior end. It becomes more transparent and cohesive. A higher degree of elasticity of the total egg content enables it to respond with local contraction to a stimulus with a hot needle.

At this point the overall dynamics of the system change fundamentally. Cytoplasmic streaming begins from the formation centre and subsumes the oscillating movements which had earlier originated in the cleavage centre. These movements include a fountain streaming anteriorly in the central axis of the egg and in a posterior direction on the periphery toward the presumptive region of immersion of the germ band into the yolk, at the onset of blastokinesis. They also encompass the differentiation centre discussed below. The activity of the formation centre is a transient but necessary step leading to the initiation of the formation of the germinal rudiment. It seems that the active principle migrates anteriorly because over a period of 12 h increasingly larger regions of the posterior pole can be deleted with no effect on the developing embryo.

The forward translocation of 'factors' from the formation centre results in the activation of the entire region in which the germinal rudiment will eventually differentiate. This area comprises the differentiation centre (*Pyrrhocoris*, Seidel, 1924; *Platycnemis*, Seidel, 1929). This centre is relatively large compared to the formation centre, and it is actually larger than the definite germ band. In some insects like *Apis* and *Tachycineta* the cytoplasm of its egg region is already identifiable at the 32-nuclei stage by its

affinity to thionine. In general, this centre becomes morphologically distinct only when cells of the periblastema, earlier evenly distributed over the egg surface, begin to congregate in this region. This leads to the formation of a monolayer of cells on both sides of the egg; however, the individual cells are still isopotential at this stage as shown by ablation experiments. In one of the next steps of development the lateral rudiments become translocated ventrally and merge to form a single rudiment.

Further experiments have given insight into the developmental processes which occur in the differentiation centre. Here we concern ourselves with specific reactions limited to the region of the differentiation centre which will subsequently become the overtly differentiated germ band, provided the formation centre is intact: the entire yolk-endoplasmic-system has become sensitized. If a small region within the differentiation centre is stimulated experimentally, the entire egg system responds with gradual, centrally oriented contractions. Thereby periplasm separates locally from the chorion providing space into which cells from adjacent periplasmic regions can flow and constitute a distinct aggregate similar to the germ band in normal development. In this way the yolk-endoplasmic-system functions like a template (Prägestock). The centre of the cell aggregation is more advanced, and it marks the site where the prothorax is going to be formed. It represents a central source from which a gradient in differentiation spreads out in all directions. This templating mechanism imposes the pattern of the germ band upon the cell aggregates of the periblastema, which was somehow prepatterned within the yolk-endoplasmic-system. In this way the physiological centre of differentiation causes the formation of a morphological centre of differentiation, first in the periplasmic layers underneath the chorion which in turn provide the cellular substrate for the germ band formation. Final contributions of the differentiation centre are made by morphogenetic movements that include complex streaming patterns which shape the longitudinal halves of the germinal rudiment and lead to their fusion on the ventral side of the egg to form a uniform germinal rudiment.

Having described the analysis of developmental systems, a few general statements about the principal method of such systems analysis may be in order. Two kinds or levels of investigations are required. (1) *Causal analyses* (individual studies of factors). We seek to elucidate sequences of reactions which depend on distinct causes and have specific effects. Such investigations could be conducted ad infinitum. However, it is essential to identify those chains of cause and effect which can yield the most reasonable explanation of developmental processes. (2) *Systems analysis* (position and function of factors in a developmental system as a whole). Among the many factors which are interconnected with each other we have to sort out those which are influencing each other in a systematic way and thus reveal a pattern of interdependence that results in successful execution of a developmental program. In doing so we uncode the 'grammar' of embryonic causes and effects in a living system, which results in the description of a morphological system based on physiological observations. The overall integration of these complex interactions constitute 'life' and shape individual organisms. Such methodical arguments shall be illustrated by two examples taken from damselfly embryogenesis. For the first example, at fertilization one finds that the male and female

pronuclei are initially separated from each other by a distance of half the egg length. The sperm nucleus has entered the anterior pole. Its path to the region where the zygote nucleus will form is complex. Only a specific spatio-temporal sequence of causes and effects will enable it to reach the female pronucleus in a predestined central location, the cleavage centre, where the first mitotic division of the zygote nucleus will take place.

The second example concerns the activation of the formation centre: energids which are descendants from the synkaryon populate the periphery of the embryo after they have migrated in a random walk through the yolk-endoplasm. Only the energid which arrives first in the formation centre absorbs the posterior cytoplasm. It seems that this cytoplasm is distinctly different from the endoplasm associated with the original synkaryon. Fusion of the cytoplasm of two different locations activates the formation centre which then allows development to proceed and realize the formation of the germinal rudiment.

The main point in recapitulating these developmental processes is the demonstration that each contains a good deal of 'morphology' in its realization. The importance of a morphological foundation for biological-physiological disciplines has become evident in the earlier deliberations on the relationship of phylogeny and ontogeny, as well as in the analysis of events concerning the study of development. These foundations must be acquired by direct observation. In judging the validity of explanations of a certain ontogenesis, and in preparation for experiments on developmental systems, one can state the following: morphological interpretations of any value for biological research will fulfil their purpose only when given objectively, i.e., derived directly from the object at hand, without embellishing them with theoretical speculations. This type of morphology is 'pure morphology'.

We can characterize 'pure morphology' by a statement of Carl Ernst von Baer concerning the process of embryonic development. He explains succinctly the coherence of the developmental progression in that 'jeweils aus dem Allgemeinen das weniger Allgemeine und so fort gibt, bis endlich das Speziellste auftritt' (from the most general pattern the less general is derived and so on, until finally the most specific appears). All embryonic dimensions are integrated in morphological ontogeny. The entire embryo fulfils von Baer's conditions as it gains shape. The embryonic body pattern that we have named the 'Körpergrundgestalt' represents the 'prototype' or the most general pattern which is characteristic for a particular species. Shaping the 'Körpergrundgestalt' is the central event in early embryonic development. The formation of germ layers which has played such a prominent role in morphological studies under evolutionary constraints is not the primary nor the most unifying event in embryogenesis. Identification of germ layers (which should be named 'blastemas' rather than '-dermis') must be based on direct observation rather than being the result of contorted derivation of a pattern element in a phylogenetic prototype. In morphogenesis based on evolutionary considerations, the mesoderm is a layer resulting from the formation of a coelom in a gastrula rather than the blastema formed in different ways in different taxa. Phylogenetic speculations of this nature make descriptions increasingly and unnecessarily complex. Rather, a terminology should be used which applies directly to observations and describes empirical findings."

Two comments may be appropriate. (1) Seidel's paradigm of insect development became both confirmed and modified by Klaus Sander, the most influential student of G. Krause. Sander provided support for a posterior signalling center in *Euscelis* by restoring the formation of a complete embryo after transferring posterior pole material to the anterior isolate. But he also argued that interactions between a double gradient with sources at opposite poles may explain what Seidel had defined as 'differentiation center'. Thus Sander arrived at a model that resembled J. Runnström's interpretation of S. Hörstadius' elegant sea urchin experiments (Sander 1976). The sea urchin model has been challenged by E.H. Davidson, and Sander's model has also since been modified such that short range inductions from a central region, i.e. Seidel's 'differentiation center', may lead to patterning of the embryo (Davidson 1986).

If Seidel's paradigm is still intact, can it accommodate the wonderfully complex developmental genetic paradigm of *Drosophila*, no doubt an insect, too? In contrast to Spemann who did not consider genes as major actors in his 'organizer', Seidel was no stranger to genetics. As disciple of Kühn, who made the first attempt to explain the color pattern of moth (*Ephestia*) wings as a chain of reactions of genes/enzymes and substrates, he was aware of the importance of genes in patterning. And, at Marburg he brought two early developmental geneticists, W. Beermann and H.J. Becker, into his institute. They conducted elegant experiments on puffing patterns of polytene chromosomes, providing solid evidence for programmed gene expression. Seidel (1972, 1975, 1976) incorporated the new insights of genetics and molecular biology in the revised edition of his three volume 'Entwicklungsphysiologie der Tiere'. Seidel has followed the breathtaking advances of *Drosophila* genetics. He tried hard to integrate the periodic expression of pattern forming genes in the *Drosophila* embryo into the sequential appearance of his 'centers'. He was unable to interpret his results as a manifestation of gene activity. Comparative molecular analyses of the

many insect embryos, experimentally studied in the Seidel-Krause school, may shed light on how we can link the classical observations to molecular mechanisms.

(2) Seidel's luminous concept of 'Körpergrundgestalten' has provided a much wider bridge: no less than the first attempt since Geoffroy St. Hilaire to define the form generation of all animals. According to a recent challenging proposal, it is the Hox-gene cluster that is responsible for the establishment of regional expression domains along the antero-posterior axis: the zootype. According to this view, the different phyla evolved by employing the same gene cluster at different times and places in the establishment of 'phylotypes'. This term is the crisp translation by Sander of Seidel's 'Körpergrundgestalt' as is fully acknowledged by the authors of the zootype proposition (Slack et al., 1993).

It seems that Seidel's principles of morphogenesis (Development's greatest unsolved mystery, *Science* 266: 562, 1994) will be with us for some time to come.

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