On the causation of animal morphogenesis: concepts of German-speaking authors from Theodor Schwann (1839) to Richard Goldschmidt (1927)

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Introduction

The quest for the causes of morphogenesis[1] originated in the realm of philosophy, and accordingly its outcome was of no practical use whatsoever – that is, until recently. This is why the progress of embryology (as that of many other disciplines) throughout its history was dependent on public and private wealth, then as now a precondition for pondering idle questions and for recording the outcome to posterity. The centers of wealth changed with the course of history, and so did the origins (or nationality in modern times) of those who made crucial contributions to developmental biology. *Aristotle*, for sure the father of embryology, lived in various wealthy communities at the shores of Greece and Asia Minor before settling in flourishing Athens. *Fabricius of Aquapendente* and *Marcello Malpighi*, who were the first to achieve progress beyond Aristotle in studying the chick embryo, worked in some of the richest cities of renaissance Italy, and *William Harvey* (*"omne vivum ex ovo"*) was attached to the court in London. Some generations later, *René-Antoine de Réaumur* and *Charles Bonnet* – the former an influential descriptive embryologist and the latter known for pushing the idea of embryonic preformation to its extremes - lived, respectively, in the heart of royal France and in a Swiss city rich from trading with that country. This city, Geneva, was also the home of *Abraham Trembley*, who – while employed in the wealthy Netherlands – was the first to perform extensive series of developmental experiments (the outcome of which gave *Hydra* its name). In summa, developmental biology from its infancy was an international venture – a fact which should not be lost from view when, as in this review (and on request of the editors), a nation's past achievements in this discipline are to be recorded.[2]

Authors of German tongue began to gain prominence only after central Europe had recovered from the devastations of the Thirty Years' war. Their first widely noted contributions interestingly were on the *theory* of embryogenesis: in mid-eighteenth century, *Albrecht von Haller* and *Caspar Friedrich Wolff* fought their famous battles over preformation versus epigenesis. Internationality, by the way, had become a personal experience by then: Haller was Swiss-born but teaching for many years at Göttingen while Wolff, of German origin, did much of his later work at the Russian emperor's academy in St.Petersburg. After

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1) Morphogenesis is among the many biological terms whose definition keeps oscillating, generally unnoticed by those who use it. The "developmentally correct" of our days restrict it to those events in development that change visible shapes, for instance the transformation of a flat epithelium into a tube or cup. Its earlier connotations (documented e.g. in the preface to Vol.1 of the "Advances in Morphogenesis", published in 1961) included all the steps leading up to such morphognetic movements, beginning with clevage or even fertilization of the egg cell. Most of these steps contribute to pattern formation, or the spatially coordinated diversification of cell fates. The ascent of the term pattern formation during the last decades was paralleled by the increasingly restrictive use of morphogenesis. Before those decades, pattern formation was a very rare term, mainly associated with geometrical patterns on butterfly wings or fur patterns of mammals. Richard Goldschmidt was the first, or among the first, to use pattern formation in its present meaning, to denote what was then generally known as "organization". Since Goldschmidt's early work forms the closing chapter of this historical review, morphogenesis is used here in the earlier, comprehensive sense.

2) Only a few general references are given in this review, in addition to the sources of figures and quotations. More facts and references can be found in several other contributions to this volume, and in the author's illustrated essays on "Landmarks in Developmental Biology", published from 1991 onward in Vols. 200 ff. of Roux's Archives of Developmental Biology. On request, the author will be ready to help with further references.

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Russia and the German states had freed themselves from Napoleon's sway some sixty years later, two youngsters from the German-speaking gentry of Russia's baltic provinces took over the lead in descriptive embryology. *Christian Heinrich Pander,* working at Würzburg, provided a thorough description of the developing chick embryo, including the three layers from which the body derives. This work attracted the attention of his friend *Carl Ernst v. Baer* who, as a professor at Königsberg (now Kaliningrad) and St.Petersburg, was to become the doyen of 19th-century embryology, and a leading exponent of several other disciplines as well. As for the causation of morphogenesis, v.Baer was the first to clearly dispense with the dogmatic alternatives of preformation and epigenesis. He stated that he could not see either, but only "Umbildung", a continuous series of transformations from the seemingly simple towards the complex, and back to the deceptively simple egg yielding the next generation.

Epigenesis and preformation, however, were defined anew and to joint use when – on conceptual foundations laid by *Hans Driesch* (1894, p. 29) – *Oscar Hertwig* introduced the concept of "preformed epigenesis" in 1916: "*The development of multicellular organisms from the fertilized egg [...] is an epigenetical process whose species-specific course is firmly determined by the preformed hereditary substance [...] which serves as its basis*". Or, as stated shortly afterwards by E.B. Wilson (1925/1928), "*heredity is effected by the transmission of a nuclear preformation which in the course of development finds expression in a process of cytoplasmic epigenesis*".

This insight, by Wilson's own testimony, rested to a large extent on the findings and concepts of developmental biologists working in Germany, a state that had achieved political unity after the Franco-Prussian war of 1870/71 and started to prosper soon afterwards. Science in the *Kaiserreich* gained additional momentum from the enlightened Prussian tradition of basing university teaching on research carried out by the professors themselves. Developmental biology in particular drew specific benefits from a unique learned institution founded at about that time. This was the famous Stazione Zoologica at Naples which owed its existence and its success to the inspiration and perseverance of a German embryologist, *Anton Dohrn*. It furthered progress in developmental biology by providing up-to-date working facilities at the seashore, but much more so by enabling the exchange of ideas between visiting scientists from all over the world. Aptly termed a "permanent international congress", it was attended by most German and American pioneers of experimental embryology and genetics. Soon afterwards yet another international venture, admittedly on a lesser scale, was to solve a major problem handicapping the nascent discipline of experimental embryology. This problem was the controlled handling of objects under the microscope. The solution came with the stereoscopic dissecting microscope, constructed at the request of *Horatio S. Grenough* (a Bostonian living in Paris) by the firm of *Carl Zeiss* (in Germany) who incorporated a feature conceived some decades earlier by *I. Porro* (an Italian), namely the prisms which turn the image upright and adapt the instrument to a wide range of interocular distances (see Sander, 1994).

The following sections will outline some crucial concepts originating with German-speaking developmental biologists in the years between 1880 and 1930. The initial section, however, will be devoted to an earlier concept, which is reminiscent of the modern concept of self assembly. Its proponent, Theodor Schwann, named it the "Theory of Cells", a term which since has acquired a quite different meaning. Schwann's developmental concepts, like some concepts described in other sections, may not directly have triggered subsequent ideas on morphogenesis, yet no doubt they form part of the historical background on which these ideas emerged.

Theodor Schwann: vitalistic concepts of morphogenesis replaced by the mechanistic "Theory of Cells" and its organismic sequel

Theodor Schwann (1810-1882) and Matthias Schleiden (1804-1881) are justly credited with the now commonplace postulate that the cell is the basic unit of all organisms. Schleiden declared this for plants while Schwann (1839), working as a museum assistant in Berlin, extended the idea to animals and announced its general validity. The immediate impact of Schwann's treatise (which won him a chair at Louvain in Belgium) did not, however, result from his careful descriptions of the cellular constitution of animal tissues and their comparison to plant cells, that is, from the "cell theory" of later generations. Rather, his *Theorie der Zellen* proposes how cells and organisms in the first place come to be. In Schwann's own words (emphases added), his *Theorie* was intended to "*prove the intimate connection between both kingdoms of organic Nature from the identity between the laws of development of the basic components [i.e. the cells] of animals and plants*".

Schwann's "laws of development" sprung from an erroneous concept that he had eagerly adopted from Schleiden, namely that cells originate within other cells or in extracellular spaces, not by cell division. This was to happen in several steps: First the nucleolus would appear. Then, as a membrane-bound shell around it, a nucleus would form and inflate. Finally another membrane would form on the nuclear surface and lift off so as to form the cell wall. Schwann believed that animal cells arise the same way, and that they are generated by some kind of (in modern terms) molecular self assembly. This process would be akin to crystal formation in the inorganic world, but was to occur in multi-component solutions in which "*attractive forces act with a certain selectivity. Not every substance in the surrounding fluid will be attracted, only some of them, partly those that are analogous to the [as yet] existing substance of the [nascent] cell (assimilation), and partly others that are chemically different. The individual layer grows by assimilation whereas for the formation of a new layer substances will be attracted that are different from the substance of the previous layer.*" A further difference to inorganic crystals was that these organic aggregates could "imbibe" water and thereby be inflated rather than dissolved.

In a brief closing chapter Schwann proposes a "Theory of the Organism" which extends this principle to the organismic level. "*Should one not be entitled to the tenet that [...] the organism is nothing more than an aggregate of such inflatible crystals?*" This would of course require that "*when many of these have arisen, they must aggregate according to certain laws so as to form a*
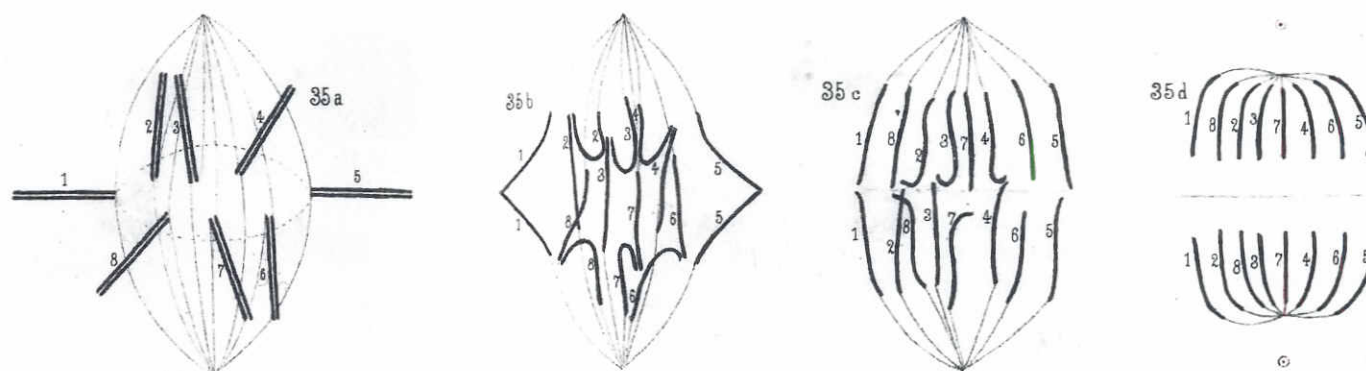
Fig. 1. The equal distribution of daughter chromsomes in anaphase, *diagrammatized – probably for the first time – in this figure of the botanist Emil Heuser (1884), student of Eduard Strasburger.*

whole system similar to an organism". Schwann supports this proposal by reference to the frost patterns on a window pane and the branched "trees" precipitating in certain inorganic solutions.

No matter how fancy these ideas may appear today, they contained a stimulating claim, namely that the formation of cells and organisms could be understood on a mechanistic basis, without recourse to teleology and vitalistic forces. Schwann strove to show "*that the basic forces in organisms conform with those in inorganic nature in so far as they act by laws of necessity and blindly without consideration for any purpose, and that they are forces that were given together with the existence of matter, like the forces of physics.*" The latter forces (as must be added for a balanced record) he held to be given by the Creator – a then quite acceptable view shared by many a physicist and chemist of the time.

Schwann's concept was perceived by his generation (the upstarts of the time – he himself was not yet 30!) as a signal of liberation from the abstruse "romantic natural philosophy" and its vitalistic sequels that had pervaded most countries of German tongue during the preceding decades. He thus opened the way for other (and more acceptable) mechanistical concepts of development that were to follow. Schwann, by the way, was well aware of the shaky ground he was treading, but he felt a strong anti-teleological urge and saw his speculations justified by their heuristic value. In his words, they offer "*the advantage that one can form certain ideas on organismic processes, which is always necessary if one wants to method-ically undertake experiments, meaning to test a concept compatible with known phenomena by calling forth some new phenomena*". An adequate "test" stimulated by Schwann's book, namely the thorough observation of cell multiplication in embryos and various tissues, proved within a few years that cells arise only by division of pre-existing cells. This bore striking testimony to the heuristic effect that Schwann had foreseen but, as so often in the history of science, he himself clung to his outdated theories until his death (some forty years later).

Walter Flemming and Wilhelm Roux: mitosis and the paramount developmental role of the nucleus

While cell division as such soon became commonplace, the fate of the nucleus during this process remained ill understood until 1879. In that year, Walter Flemming (1843-1905), professor of anatomy at Kiel, meticulously described nuclear division in the skin of newts (which are ideal on account of their very large chrosomes). He noticed that the chromatin of the "typical" nucleus changes into a string (mitos in Greek, hence his term mitosis) that would subdivide into a number of loop-shaped segments. These "nuclear threads", named chromosomes a decade later, then would split lengthwise. The halves would move towards the poles of the "achromatic" spindle, to transform there into the chromatin of newly forming daughter nuclei and cells. Flemming being a pathologist, the main aim he proclaimed in his pioneering paper was to establish cytological criteria by which cells integrated into tissues could be distinguished from rampant cells. He found that tissue cells (e.g. those in his newt epithelia) when dividing exhibited only the different stages of mitosis as described, while in migrating cells the chromatin preparing for cell division would often undergo clumping and fission of the whole mass. Flemming was happy with finding this difference – and did not bother to drop even the slightest hint at the paramount *biological* importance of mitosis.[3]

This importance became evident within a few years when several cytologists, Fleming among them, recognized that the two halves of each split thread were regularly moving to *opposite* spindle poles (Fig. 1). In 1883 Wilhelm Roux (1850-1924) (Fig. 2), anatomist at Breslau (now Wroclaw), took this as the basis for the first theoretical treatise on mitosis. By ingenious albeit complicated reasoning, he held the chromosomes to be highly complex despite their uniform appearance: "*The apparent homogeneity of the whole chromatin mass [...] will not deceive him who realizes that we look at the molecular events like looking down on a large factory from a balloon floating at the highest elevations [...], and that therefore the most diverse can appear*

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3) One reason for this omission becomes apparent in the preface of Flemming's book of 1882, where he writes: "He who should search in this new book for novel catchwords [...] will note the absence of any hypotheses or theoretical views on cell division. All the constructions so far made to this end appear like groping in a dark room where as yet nothing certain has been felt. They will have to be continued; however, in the present attempt at conveying [to the reader] today's factual knowledge I wanted to stick to the tangible."

homogeneous to us. [...] For certain the complicated [mitotic] *behaviour of the seemingly homogeneous substrate* [i.e. the chromatin] *requires the conclusion that its structure must be complex".*

The developmental implications of this insight were summed up in Roux's last paragraph: "*The fact that for nuclear division such complicated arrangements have been made* [....], *which are lacking for the cell's body, lets one conclude that the cell's body is to a much larger extent made up of equivalent componenents thán is the nucleus; and from this follows that for the development of the embryo, and perhaps also for the regenerative potential of lower animals, the nucleus is more important than the cell's body, a conclusion that stands in complete agreement with recent results concerning the process of fertilization*"[4].

As has been described quite often (and often by his own pen), Roux went on to define and advertise a new discipline which he chose to call *Entwickelungsmechanik*. This term was an unfortunate choice because the Kantian definition of "mechanics" (= natural causation) implied by Roux was obsolete already in his time. It has since generated endless misunderstandings, yet Roux's many programmatic writings on the problems, aims and concepts of his new discipline can justly be considered the birth documents of developmental biology. In order to foster his brainchild (he did little experimental work himself during these years), he founded in 1894 the *Archiv für Entwickelungsmechanik* - which later was to carry his name – and with a strong hand acted as its editor for almost thirty years (see Counce 1994).

August Weismann: Germ plasm, germ line and differential somatic mitoses

Returning briefly to Roux's treatise of 1883, be it noted that most of its pages are concerned with the *equal* distribution of the daughter chromosomes (and hence the nuclear qualities) onto the daughter cells. It is only on one or two pages that he discusses the possibility that mitosis could *also* serve for *unequal* distribution. Yet this is what the textbooks will forever associate with his (and Weismann's) name, owing to a widespread misinterpretation of Roux's terms "qualitative" and "segregation". In the present writer's view, Roux must have inserted the respective paragraphs into an otherwise complete manuscript that argued for the equal distribution of all chromosomal components – probably after he had obtained, in that very spring, his famous "half embryos". The "mosaic work" apparent in these embryos was ascribed by Roux only in very general terms to unequal mitoses, and at times he suggested various other causes.

August Weismann (1834-1912) (Fig. 3), not Roux, should consequently be considered the true and unflinching proponent of unequal chromatin segregation. In his younger years Weismann was an outstanding descriptive embryologist whose work on dipteran development can justly be called epochal; it lives forth in terms like "pole cells" and "imaginal discs". Thereafter, and perhaps from the strain of his excessive use of

Fig. 2. Wilhelm Roux.

the microscope, Weismann's eyesight failed, restricting him to theoretical work for many years. During these years all his thinking was inspired and directed by Darwin's *Origin of Species* that had come to his knowledge a few years after its publication. By the time when Weismann retired from the chair of zoology at Freiburg (which by then he had held for close to half a century), he had contributed fundamental concepts to developmental and evolutionary biology as well as to incipient genetics. Some of his concepts no doubt were mistaken or exaggerated, but their impact on the future course of biology is evident from their being rendered in the introductory chapter of almost every relevant textbook.

Weismann's key concept was the germ plasm (*Keimplasma*), defined as the hypothetical molecular structure governing all heritable traits of an organism. It is essentially the equivalent of the modern genome, whereas the term "germ plasm" nowadays means something entirely different (the cytoplasmic germ line determinants). On the evidence of mitosis and of fertilization (see Roux), Weismann localized his germ plasm in the chromosomes, or idants as he called them. This insight, by the way, precluded the heritable transmission of acquired characters, and thus trans-

4) Fertilization came in here because in the years immediately before, Oscar Hertwig and Eduard Strasburger had declared that the nucleus is the only persisting component of spermatozoon and pollen tube, respectively.

Schwarz   Ishikawa   Fritze   Maurer Stuhlmann   Riegel

Eylmann   Korschelt   Gruber   Schäfer

Fig. 3. Studio photograph of August Weismann (center) with his assistant and Ph.D. students, adequately equipped.

formed Darwinism into Neo-Darwinism or Weismannism as it was called in England for some years.

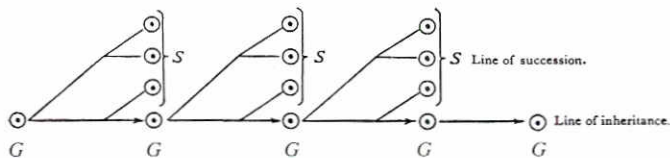The developmental aspect of Weismann's concept comes in with the germ line (*Keimbahn*), consisting of the succession or line of cells that connect the zygote with the gametes of the

Fig. 4. August Weismann's concept of the split between germ line (G) and somatic cells (S), *as illustrated by Wilson (1896).*

ensuing individual, and in each mitosis split off a somatic cell (Fig. 4). Weismann's developmental problem was that the somatic cells and their descendants sooner or later would each perform only one a small part of the tasks required for producing the individual's body. If all somatic cells should receive and maintain the same germ plasm, how could they come to perform tasks so different? Weismann (1892) chose to account for this by envisioning unequal or differential mitoses, which were to provide the daughter cells with (partly) different selections from the sum total of heritable qualities, as shown in a highly diagrammatic way in Figure 5. The possible alternative, differential gene activity (in modern terms), was dismissed by Weismann with a disarming combination of Darwinian creed and Ockham's razor: "*Why should Nature, who lets parsimony act everywhere, afford*
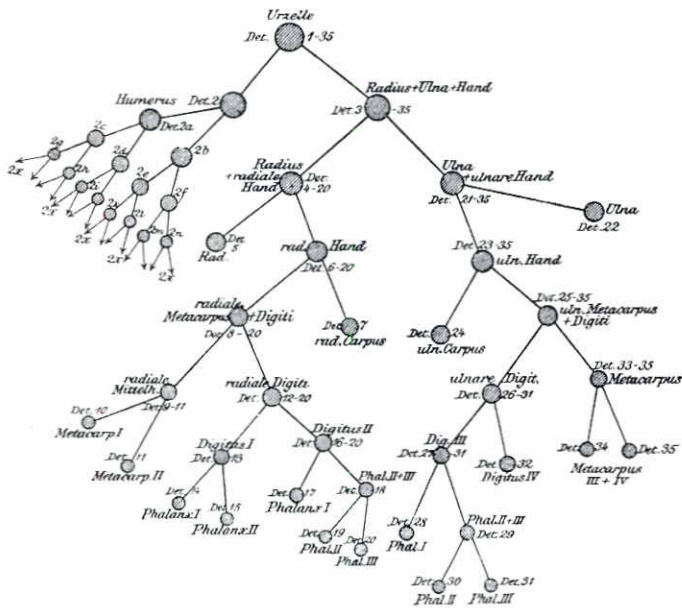
Fig. 5. Diagram showing Weismann's principle of cell diversification by unequal nuclear divisions; *note that Weismann himself declared this as grossly simplified. The chromatin of the cell giving rise to the anterior tetrapod extremity comprises the molecular 'determinants' numbered 1-35. These determinants are then split up between daughter nuclei during subsequent divisions, until individual cells retain only a single determinant which then directs their contribution to the whole. From Weismann (1892).*

the luxury to endow cells with all the determinants in the germplasm if a single kind suffices?"

Of the problems inherent in his concept, those posed by regeneration (of which Weismann was as aware as his critics) were yet the easiest to circumvent by means of additional ad hoc-assumptions. The most formidable problem rested in the fact that the various specializations of somatic cells cannot arise randomly – they evidently are strictly coordinated in space and time. Weismann ascribed this marvellous feat to the complex but constant spatial structure of the zygote's germ plasm, which saw to it that each of its special components was parcelled out to the respective daughter cells at the right time and place. It is here that Weismann meets the Roux of the textbooks, for the unequal mitoses that Roux had briefly discussed would be fraught with the same problems. However, whereas Roux in his later theoretical writings envisioned a lot of coordinating interplay between different parts of the embryo, that possibility was alien to Weismann's thinking (or willfully neglected by him).

If Weismann was wrong in crucial aspects of his concept, he was right (like Schwann) in stressing its heuristic merits. At some occasion he addressed his audience on this topic as follows (Weismann 1886): "*Unconnected facts placed side by side are of as little value as are theories lacking firm support. Without hypotheses and theories there will be no scientific research. They form the sounding line by which we probe the depth of the ocean of ill-understood observations, in order to set the further course of our research vessel. [...] May you accept in this sense the guidepost, or compass, I have presented to you today. No matter whether it should be destined to be replaced by a better*

one some day: if only it proves able to guide research for some stretch of its way, it will have served its purpose". Which evidently it did.

Hans Driesch: fundamental findings taken to defy all mechanistic explanations

Hans Driesch (1867-1941) (Fig. 6) was the heir of financial fortunes that in this as in any other respect made him the most independent of German developmental biologists. With him we switch to concepts based on systematical experiments involving embryos. It is true that earlier on Wilhelm Roux had explored and defined the conceptual foundations for experimental research on embryogenesis. Yet his own experiments were sporadic enterprises and in several respects fell short of Driesch's.

Driesch started his experiments under the influence of Roux's early work. He carried them on for nearly twenty years and then traded them for philosophy. There, as the founder and preacher of neovitalism, he earned much more public acclaim (including a chair at Leipzig University) than he had earlier by
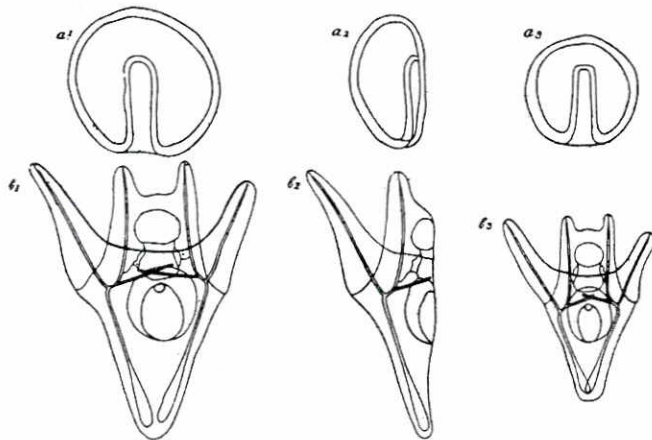

Fig. 6. Hans Driesch.

FIG. 5.—ILLUSTRATION OF EXPERIMENTS ON ECHINUS.

a_1 and b_1. Normal gastrula and normal pluteus.
a_2 and b_2. "Half"-gastrula and "half"-pluteus, that *ought* to result from one of the first
  two blastomeres, when isolated, according to the theory of "evolutio."
a_3 and b_3. The small *but whole* gastrula and pluteus that actually *do* result.

Fig. 7. Sketch and legend by Hans Driesch contrasting development of a blastomere isolated after first cleavage with the result to be expected in keeping with Weismann's concept and Roux's half-embryos; *note that "evolutio" here (as through most of the 19th century) means the ontogenetic unfolding of invisibly preformed structure. From Driesch (1908).*

his embryological experiments – or, for that matter, by his stupendous "Analytical Theory of Organismic Development". This treatise (Driesch 1894), which in places is amazingly clairvoyant, was evidently (and understandably) beyond the grasp of most contemporaries. Nonetheless, Driesch's experiments agitated and stimulated his fellow developmental biologists at least as much as did Roux's writings – witness Theodor Boveri, for whose work on the constitution of the nucleus and its role in sea urchin morphogenesis Driesch provided several leads and incentives.

As has been described innumerable times, Driesch in 1891 managed to isolate individual sea urchin blastomeres by shaking
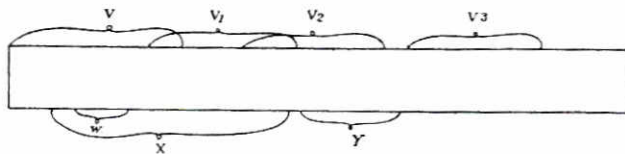

FIG. 14.—AN "HARMONIOUS-EQUIPOTENTIAL SYSTEM" OF WHATEVER KIND.

According to the "machine-theory" of life this system ought to possess a certain unknown very complicated machine *in its completeness :*
  (*a*) in its total length,
  and (*b*) in each of the equal volumes v, v_1, v_2, v_3 and so on,
  and (*c*) in each of the unequal volumes w, x, y, and so on,
  and (*d*) in every imaginable volume, no matter of what size.
Therefore the "machine-theory" of life is absurd.

Fig. 8. Sketch and legend by Driesch, meant to refute all mechanistical explanations of ontogenesis. *He coined the term "harmonious-equipotential system" after finding that isolated blastomeres can each develop like their mother cell, the egg cell. This cell was considered such a system because its parts (the future blastomeres) are supposed to possess the same potencies as the whole egg cell, and express this by producing harmoniously (i.e. properly) proportioned dwarf larvae. The claims to equipotentiality embodied in the figure are evidently exaggerated, and so is the conclusion. From Driesch (1908).*

early cleavage stages. To his surprise he found that some blastomeres produced a complete (albeit small) larva rather than the half larva that he had expected in view of Roux's half-embryos (Fig. 7). He immediately announced that sea urchin eggs can give rise to twins while actually he could not know whether any two of his swimming dwarf larvae derived from the same zygote. In this instance, however, his daring generalization (supported by just a single siamese twin embryo of uncertain origin) proved right in the end.

Mistaken, however, was Driesch's claim – again based on indirect evidence – that *any* blastomere isolated from the eight-cell stage could yield a complete (albeit minute) larva. Yet the totipotency of vegetal *and* animal blastomeres implied in this claim was crucial for Driesch because it lead him into denying any kind of preformed machinery in the egg cell (Fig. 8). This denial in turn provided him with a seemingly irrefutable starting point for his "proofs of vitalism" and for proclaiming a transcendental force, named entelechy, which (as set forth by him) was to handle the embryo like a railway driver his steam engine – letting her run on mechanistic principles but being capable of interfering purposefully when something threatened to go awry.

Driesch's vitalism was annoying (to say the least) to his fellow developmental biologists, who mostly were mechanistically inclined, and his high-brow demeanour was not exactly suited to mellowing their feelings. Yet the ensuing, largely negative judgements about his concepts should not obscure the fact that in his early years (he wrote the "Analytical Theory" at age 27!),
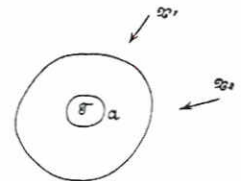

Fig. 9. Sketch by Driesch, to demonstrate that reaction to a stimulus requires some predisposition in the reacting cell, and some intermediary in the cytoplasm for mediating the signal to the nucleus; *the table was translated from the German original by the present author. X_1 and X_2 are two stimuli acting successively on the cell. A (a in the figure) denotes the cytoplasm, T the "totality of elementary potentialities, i.e. the nucleus". In essence, the first stimulus transforms the state of the cytoplasm. This activates part of the nuclear elements (i.e. individual catalysts). These in turn transform the cytoplasm to a new state which makes it receptive for stimulus X_2. From Driesch (1894).*

Driesch's was an inspired and brilliant analytical mind - witness his prescient claim for what we would call receptor and second messenger functions in the cytoplasm of reactive cells (Fig. 9), and his reflections on embryonic induction.

The concept of "chemical" induction (Fig. 10) probably sprung from Driesch's intellectual interaction with Curt Herbst, a life-long friend whose work on the effects of inorganic ions, rather less brilliant but incomparably more painstaking, proved of lasting value. It was to provide developmental biology with some much-used means for dissociating cells (just deprive them of calcium) and for shifting the developmental potential of blastomeres (expose the egg to lithium or rhodanid ions).

Of Driesch's many insights, whether right or wrong, one of the earliest was widely accepted in his time and has lately experi-
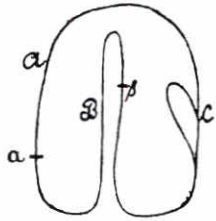
Fig. 10. Sketch by Driesch illustrating his vision of localized "chemical induction". *"If we imagine a larva formed of the three organs A, B and C [note that A is printed as a large a] and remember that A, B and C differ in their chemical constitution, the possibility must be admitted that the C-substance acts on organ B so that where it first reaches B – for instance in the course of diffusion through the surfaces and the body liquids between C and B – it will release in B the formation of some organ to which the latter was predisposed; this therefore would occur opposite to C, at ß. It should be noted that in this case the position of ß would change with a change in the position of C; ...". This statement clearly would be applicable to neural induction in amphibians as demonstrated 30 years later. From Driesch (1894).*
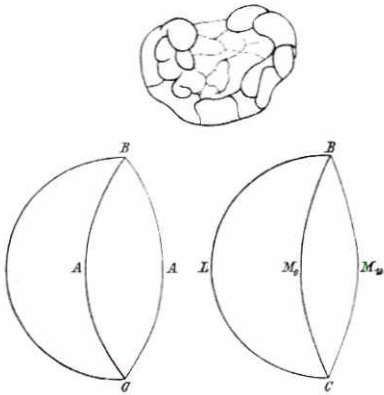

Fig. 11. Sketch by Driesch, demonstrating that some cell fates must have changed when a pluteus develops from a blastomere isolated after first cleavage. *Development of such blastomeres usually leads to a half-blastula (top) which then contracts its free rim so as to close up. The bottom figures represent two ways by which this could occur. If M_o and $M_{u'}$ two points at the future midline, were to meet when the open rim fuses, they would find themselves forming the right-hand edge of the larva when L is intended to mark the (persisting) left margin. If, on the other hand, C were to move upwards and meet B, the original left flank (L) would have to form the lower pole region. Driesch writes in 1891: "Whichever twist one gives to this matter, one cannot get around the profound difference in the roles that a given part of the germ has to play depending on whether a single individual arises or two ...". From Driesch (1891).*

enced re-incarnation in the "positional information"-concept that Lewis Wolpert developed independently. This insight is Driesch's *"Fundamentalsatz"*, formulated in 1892: "*The relative position of a blastomere within the whole will probably in a general way determine what shall come from it; if it be situated differently, then it will give rise to something else; or stated in another way: its prospective relation* [fate] *is a function of* [its] *place"*. Figure 11 shows one of the observations on which Driesch based this claim, a claim which is likely to remain valid and useful – albeit with certain restrictions, the first of which were pointed out by Theodor Boveri.

Theodor Boveri: the complex developmental machine resides largely in the nucleus

The profound influence of Theodor Boveri (1862-1915) (Fig. 12) on leading developmental biologists in his and the next generation is perhaps best documented by two books that their authors dedicated to him or his memory, respectively. These books were arguably the most important in developmental biology before the molecular age: Wilson's "The Cell in Development

Fig. 12. Theodor Boveri.

and Inheritance" (1896) and Spemann's "Induction and Development" (1938, German edition 1936). As Boveri's work will be discussed elsewhere in this volume, we shall concentrate here on a few basic concepts.

Boveri spent most of his scientific career at Würzburg, not far from his birthplace. He was outstanding both in his observations and in their interpretation. As for observations, he discovered (or independently rediscovered) that the egg cell of *Strongylocentrotus* (now *Paracentrotus*) *lividus* forms a subequatorial ring of pigment, and that the animal-vegetal axis - defined by the location of germinal vesicle and polar bodies - throughout early development maintains its orientation with respect to this ring. This enabled him to show that after experimental derangement of blastomeres the archenteron would constantly invaginate in the vicinity of the micromere-forming region. If an embryo that was deprived of this vegetal pole material did manage to gastrulate, the archenteron would for sure invaginate in the region abutting the former pole region.

Boveri concluded that the egg cell, contrary to Driesch's claims, is far from being isotropic and equivalent in all its parts. Neither, however, does it embody a preformed mosaic of determinants, with (for example) the pigment-bearing layer being determined to yield the mesoderm. Rather, the vegetal pole must be considered a center of first differentiation from where the var-

ious cell tiers would receive their determination. Whatever might account for this specific ability must be strongest near that pole, and fade gradually away with distance from it. This anisotropy would permit a mechanistical explanation of morphogenesis, in which "*the simple differentiation of the cytoplasm serves to set in motion the machine whose essential and probably most complex mechanism rests in the nuclei*" (Boveri 1902).
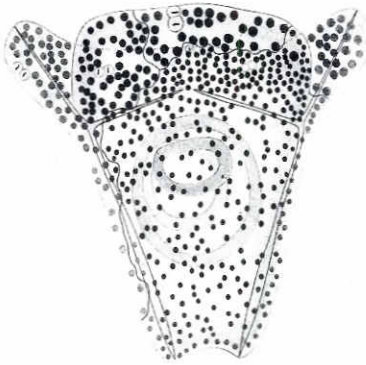

Fig. 13. Drawing by Theodor Boveri, showing a pluteus larva developed from a sea urchin egg fertilized by two sperm. *The egg cell was divided into three blastomeres at first cleavage (Simultandreier) and consequently the larva consists of three territories (or clones in today's terminology) marked by different nuclear sizes; in most cases at least one of these clones would deteriorate and cause the larva to decay. From Boveri (1907).*

When Boveri invoked the nuclei as the key to understanding development, it was not on the speculative arguments of Weismann or Roux. Rather, it was on his own most ingenious reasoning, triggered by his *Ascaris* work and by some hurried observations of Driesch on sea urchin embryos. Driesch had noted that eggs fertilized by (assumedly) two spermatozoa tended to simultaneously cleave into four instead of two blastomeres during first cleavage (forming the so-called *Simultanvierer*), and that their subsequent development became increasingly aberrant. Realizing that three gametes could not possibly provide all four daughters of the dispermic egg cell with the normal amount of chromatin, Driesch ascribed the ensuing aberrant development to insufficient amounts of chromatin per cell.
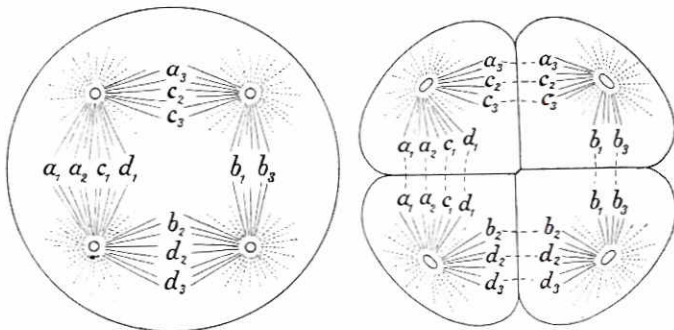

Fig. 14. Diagram by Boveri of the *Simultanvierer* type division of a dispermic sea urchin egg, to illustrate the chance distribution of the three chromsome sets among the four spindle poles derived from the two spermatozoa. *The chromsome sets, two from the sperm and one from the egg's pronucleus, are simplified so as to comprise only three chromsomes, marked a, b and c. From Boveri (1904).*

Boveri took up the dispermy problem some years later, but with a different conceptual background. Driesch refused to ascribe any fixed structure to the nucleus – he considered it a storehouse of enzymes with no spatial order in it, and he let it be known that he saw no reason for assuming that structural complexity should be hidden in the chromatin. Boveri, by his work on *Ascaris* chromosomes and sea urchin merogony, had come to feel that this view was wrong, and he realized that the dispermic *Simultanvierer* embryos provided the means to check on the functional equivalence (or otherwise) of the chromosomes. His merogonic plutei had shown him that nuclear size depends on the amount of chromatin present, and that haploid nuclei (and cells), which have only half the volume of their diploid counterparts, could support larval development as well as diploid cells. Taken together, these findings excluded chromatin quantity as such – at least at or above the haploid level – from the possible causes of these developmental anomalies.

Looking at larvae from dispermic eggs, Boveri found them to be mosaics of territories marked by different nuclear sizes which ranged mostly above the haploid level (Fig. 13). The number of territories – or clones in today's usage – was dependent on the number of blastomeres (mostly four, sometimes three) simultaneously produced in first cleavage. His earlier experience with cleavage mitosis told Boveri that the different classes of nuclear size must result from random distribution of three chromosome sets between the four spindle poles ensuing from the centrosomes of two sperm (Fig. 14).

If so, he reasoned, and if the individual chromosomes of a haploid set differ in functions required for development, then the different clones should greatly vary in their developmental fates. Testing this idea by separating the three or four blastomeres
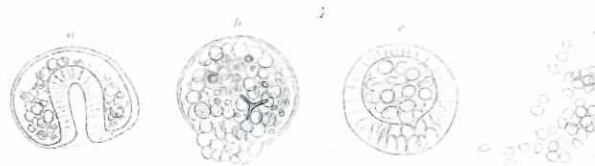

Fig. 15. Drawing by Boveri, showing the endproducts of development of the four isolated blastomeres of a *Simultanvierer* (cf. Fig. 13). *The progeny of the individual blastomeres of the same egg survive up to very different stages and then decay under a wide range of symptoms. Drawing from Boveri (1907).*

produced by the aberrant first cleavage division, Boveri found what he had suspected: they yielded a wide range of developmental anomalies which were rather independent of nuclear size (Fig. 15). He concluded: "*Thus what remains is that not a certain number, but a certain combination of chromosomes is required for normal development, and this cannot but mean that the individual chromosomes must possess different qualities*" (Boveri, 1902). This result and its satisfactory simulation by Boveri in a kind of statistical "chance machine" was judged by Wilson as Boveri's "*crowning achievement, whether in respect to the excellence of method or the importance of result*" (Wilson, 1918).

The essential difference between this achievement and Driesch's claims (cf. Fig. 8) was summed up by Boveri (1902) in the following words: "*... one can take away randomly from the*

young echinid germ 'any nuclei' (as shown by Driesch), but not 'any part of the nucleus'. To take away something from the nucleus, that [feat] has not even been attempted in Driesch's experiments; my own, however, which accomplish this, teach us that the nucleus - to which we now can ascribe any degree of complexity - behaves exactly as postulated for a 'machine' by Driesch in his considerations."

While Driesch, owing to his personality and life-style, failed to form anything resembling a "school" in developmental biology, Boveri attracted many doctoral students (some, his future wife included, even from the United States). Two of these students deserve special mention in any history of developental biology: Hans Spemann and Leopold v.Ubisch. They extended quite different sectors of Boveri's work on the "morphogenetic machine". No less different were their lives and consequently their memory among later biologists. Spemann was exempted from military service in the First World War, and during this time (spent at the Kaiser-Wilhelm-Institut für Biologie at Berlin-Dahlem) laid much of the foundations for the work that won him the Nobel prize in 1935. Von Ubisch, by contrast, had served with distinction in the army during the war but nonetheless was driven from Germany by Hitler's hordes because he refused to part with his Jewish wife.

Leopold v. Ubisch: gradient levels coordinate gene action

Leopold v. Ubisch (1885-1965) had worked for decades on sea urchin development and, although overshadowed in this field by Sven Hörstadius, had become a full professor at Münster. However, his main conceptual breakthrough, the linking of gene activity to different gradient levels, came in his Norwegian asylum. It was published in German during the postwar years and in a highly speculative context. Hence it had few readers – among them the present writer who transposed it to insect embryogenesis.

Based on his own work and that of the Swedish school, v. Ubisch was a strong believer in the role that cytoplasmic gradients play in pattern formation; "non-Childian" gradients, one may be sure, because he repeatedly exposed the weak points of the largely metabolic gradient action proposed by C.M. Child. But in contrast to most experimental embryologists of the 1930s, v.Ubisch fully acknowledged the role that the genes of Morgan's school must play in early development – and endeavoured to conceptually link patterned gene activities with cytoplasmic gradients.

To illustrate the outcome, v. Ubisch (1953) took recourse to alpine plant zonation: *"How is it that at different levels of elevation on a mountain different floras are thriving? Probably because the hillside cuts through a gradient of temperature, to whose different levels are assigned corresponding plants. This correlation can also be expressed the following way. The climatic gradient of the mountain exerts selection: of the multitude of plant seeds offered to them, each level in the climatic gradient selects those that fit it. Exactly this happens in the embryo: the cytoplasmic gradient at each of its levels selects - from the total genome at its disposal in all nuclei - those genes which are coordinated to it'.*

Fig. 16. Hans Spemann.

Hans Spemann: analyzing induction while neglecting the genes

The achievements of Hans Spemann (1869-1941) and his school, told often and from different viewpoints, will be discussed elsewhere in this volume. Here only one point will raised, namely Spemann's abstinence from discussing genes in the context of development. This topic is not at all new, but it highlights the difference between Spemann's concepts and those of the two scientists commemorated in the adjoining chapters of this review, Leopold v. Ubisch and Richard Goldschmidt.

Spemann was of course aware of Mendelian genetics but apparently did not make any effort to incorporate gene action in his developmental concepts; he avoided using the term gene (which after all was first coined in German) even in those contexts where heritable influences on cell fates could not possibly be denied, as in the chimeric oral structures obtained in transplantations between urodelean and anuran species by Oscar Schotté[5]. This self-imposed restriction, which seems to have

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5) That the results of these and the earlier organizer transplantations could be seen in the conceptual framework of gene activities is documented in a letter from Carl Correns (one of the rediscoverers of Mendel's laws) to Hans Spemann, found recently by Peter Fäßler (1995). Considering the species-specific character of the patches that are integrated into a joint organ anlage, Correns wrote in 1923:" This is the contrast between what we assume to be genes localized in the chromosomes, and that which provides for the unfolding of the [activity of the] genes in the correct sequence ..."

influenced developmental research in Europe for decades, may have resulted from a combination of causes, of which two seem well documented. According to his own testimony, Spemann owed much to the writings of his predecessor Weismann, but their speculative character had raised antipathy or even contempt in Spemann's own generation, which reacted by striving to do solid experiments. Thus Spemann – second to none in conceiving the experimental techniques required – clung to his experiental results, interpreting them as cautiously as possible rather than embedded in a far-flung framework. In his defense it should also be recalled, in these days brimming with work on developmental mutants, that in those days genetic data that might have revealed patterning mechanisms were still lacking, except for a single embryonic patterning mutant, the leiotropic pond snail. This, however, was not a compelling instance either, because the genetic defect might not affect the patterning machinery as such but only a superimposed handedness.

The other evident reason for Spemann's abstinence from, or even antipathy to, genetics was the success of the geneticists themselves. In the view of Spemann (and of some Americans, notably Harrison), they planned to encroach upon territory laboriously cultivated by experimentalists who were about to reap their harvest. In the crucial year 1924, when Hilde Mangold's dissertation describing the organizer effect was in the press, Spemann addressed the newly founded German genetics society on the relation between genetics and developmental physiology. His closing words, which invoke cytogenetics as a precedence, clearly enough express his fears: "*It was an important moment for the science of inheritance when the trails of* [Mendelian] *hybrid analysis and of cytology, separate at first, came to fuse. Amazing results have since been achieved, and it is truly not from a feeling of unsuccesssful labours but rather in the knowledge of superb powers of appropriation that inheritance research now is on the outlook for new liaisons. Their eyes now have fallen on us, on Entwicklungsmechanik ...*". Similar feelings were to arise, albeit not voiced in writing, in the community of experimental insect embryologists some fifty-odd years later when *Drosophila* geneticists intruded in their field and completed the take-over envisioned (and dreaded) by Spemann.

Spemann's tradition carried on: Otto Mangold and Friedrich Seidel

Spemann's influence on developmental biology was spreading not only on its own but became also internationalized by quite undesirable means. Several of his most able students – Viktor Hamburger, Salome Glücksohn, Johannes Holtfreter – had to flee Germany when the Nazi movement took over, or left the country on their own accord. They came to fame abroad with their own concepts, but only after years of distress and with the emotional scars that remain after seemingly stable human relations have been canceled willfully. Among those who stayed in Germany and accomodated to the political situation (at first rather willingly), the most influential were Otto Mangold and Friedrich Seidel. Seidel was no direct descendant of Spemann's school, but he took pride in its traditions and acknowledged its influence on various occasions.

Otto Mangold (1891-1962, married to Hilde Pröscholdt since 1921), Spemann's successor both at Dahlem and in Freiburg,

carried on Spemann's tradition and extended it in several directions. He much refined the concept of embryonic induction, by experiments that have their firm place in textbooks and history. Mangold's work (and Holtfreter's techniques) paved the way for the biochemical approach to induction by Heinz and Hildegard Tiedemann (the latter Mangold's PhD student). In pioneering efforts of truly herculean dimensions (see Tiedemann *et al.*, 1995), they identified biochemical fractions that had highly region-specific inducing properties. However, in the molecular race for inducer molecules now going on, their competitors rarely take pause to remember these early achievements.

Friedrich Seidel (1897-1992) was the first doctoral student of Alfred Kühn (one of August Weismann's last students). After completing his thesis, in which he described embryogenesis in the linden bug *Pyrrhocoris*, Seidel worked in Otto Mangold's (formerly Spemann's) division at Dahlem. Together they fused pairs of newt embryos during first cleavage, demonstrating that already at this time the prospective organizer must be localized to a restricted sector of the dividing egg cell. On his own, Seidel during this period turned to experimental insect embryology, the discipline which he was to shape for decades by his concepts and his strong personality (see Counce and Waddington 1972); more than anyone else he was instrumental in showing that insect eggs are far from being developmental mosaics (as held by some influential text-books of entomology until quite recently). In his first experimental paper, announcing the dynamic influence of the *"Bildungszentrum"* (activation centre) on the *"Differenzierungszentrum"* (center of differentiation, a term used earlier by both Boveri and Spemann), Seidel acknowledged the *genius loci* of Dahlem: "*To have set out on these experiments with such clear questions in mind would not have been possible, had not Spemann's concept of the organizer in Triton embryogenesis been available*".
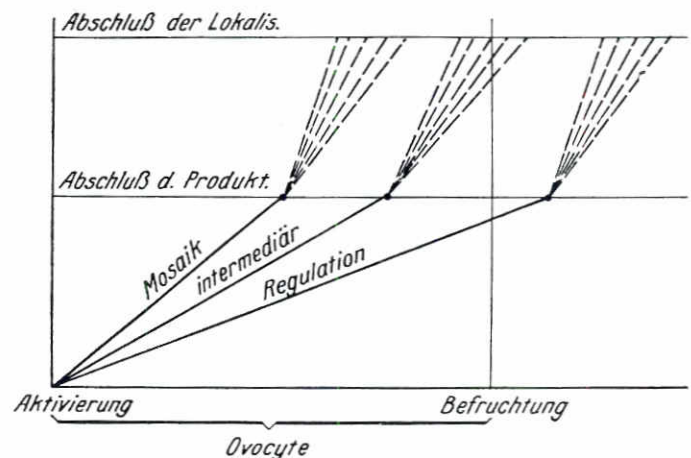

Fig. 17. Diagram by Richard Goldschmidt explaining the difference between mosaic and regulative eggs by the relative timing of synthesis (bold lines) and localization (broken lines) of maternal gene products. *These events start with activation of the respective genes early in oogenesis and, depending on type of development, may or may not continue into early embryogenesis. Aktivierung= activation of genes, Ovocyte= oocyte, Befruchtung= fertilization, intermediär= intermediary, Abschluß d. Produkt./Lokalis.= end of production and localization, respectively, of the "form-generating substances". From Goldschmidt (1927).*

Richard Goldschmidt: early concepts of differential gene activity

Richard Goldschmidt (1878-1958) was a colleague of Spemann and Mangold at Dahlem before being driven into exile by Nazi politics. With a personality reminiscent of Driesch's, but free from any vitalist inclinations, he proved both stimulating and at times oppressive. Consequently he had few followers, but these were highly capable, witness his one-time assistant Curt Stern. Stern, too, was later expelled from Germany – again to the great loss of German developmental biology. Goldschmidt's work on quantitative and progressive gene action, using mainly the development of sexual characters in lepidopterans (which he studied in both Germany and in Japan), was widely recognized in the pre-war period. Much of the concepts sparked by these investigations left its mark in his *Physiologische Theorie der Vererbung* (1927), a work that in more than one respect appears akin to Driesch's *Analytische Theorie* – including some scorching polemics, in Goldschmidt's case against the indifference of the Morgan school towards the ontogenetic role of the genes (and specifically towards Goldschmidt's own ideas on this topic).

In the present context, it is Goldschmidt's concept of gene action in embryonic (pre-) pattern formation that deserves atten-

Fig. 18. Goldschmidt's scheme of maternal and zygotic gene activity in insect development. *During oogenesis (the three figures at the top) different "form-generating substances" are synthesized and get localized (see arrows) on the basis of their own properties. When cleavage nuclei (Furch.) are spreading and blastoderm cells have formed (the two figures at the bottom), the form-generating substances act as substrates which permit (and thereby automatically trigger) the catalytic activity of those genes that can metabolize them, thus initiating the next step of cell differentiation. The letters indicate "form-generating substances" for the following parts: A dorsal side, B ventral side, C germ line cells, D brain, E legs. From Goldschmidt (1927).*

tion. It was based on the view, widespread by then, that genes act catalytically, and on Julian Huxley's recently introduced "chemodifferentiation" as a basic process in early embryonic patterning. Goldschmidt proposes that the generation of spatial patterns is a two-step process, with gene effects first resulting in the production of certain "form-generating substances" that thereafter become localized by some epigenetic process. The earliest activity is exerted by maternal genes. The localization of their products occurs subsequently, its time course depending on the type of development. In "mosaic eggs" localization is complete by the time when embryogenesis begins, whereas in regulative development the process of product localization, and even part of the genes' catalytic activity generating the products, occurs after the onset of embryogenesis (Fig. 17).

Goldschmidt's most graphic illustration (Fig. 18) features the insect egg which he, like everyone before the impact of Seidel's work, considered representative of the extreme mosaic type. Here, the maternal form-generating substances get localized in the oocyte during oogenesis. Some of them are thought to enter the oocyte in succession from the nurse cells, which would cause a sort of layering in the ooplasm. When embryonic cells were formed, the embryo's own (= zygotic) genes would take over and by their catalytic activities progressively increase chemical and cellular diversity.

It is only the lesser details which unmistakably reveal that these concepts were developed almost seventy years ago. One such detail is Goldschmidt's mechanism of sequential gene activation. "*What could be envisioned specifically with respect to this activation? Should we for instance believe that the genes until then are by some kind of inhibition prevented from starting their catalytic activities, and that these inhibitions vanish at that* [right] *moment?*" Goldschmidt discards this idea in favour of a seemingly simpler one: since genes are catalysts, they will of necessity start acting once their specific substrates become available. The catalytic capability of all the genes is always present in any nucleus, but each gene starts acting only when – and because! – its substrate is getting available. Thus the "form-generating substances" seen pre-localized in Figure 18 are to represent substrates which would cause suitable catalysts (that is, the respective genes) to direct their chemical modification once the cleavage nuclei had reached those parts of the egg cell.

We turn back for a moment from Goldschmidt to the other visionary commemorated in this review: Hans Driesch. In 1894 – ten years before lens induction was demonstrated, and thirty years before the paper of Spemann and Hilde Mangold – Driesch had some vision of localized induction, albeit mistaken in many background details which could not be known or resolved at that time. Similarly, Richard Goldschmidt formed his vision of the role that genes play in early embryogenesis long before the means for testing this role (and amending his views) became available in our days.

Epilogue: the rise and fall of German developmental biology

Reviews on a nation's contribution to whatever topic entail the risk of lopsided representation. The series of important conceptual break-throughs ascribed here to German-speaking developmental biologists and their impact on developmental biology
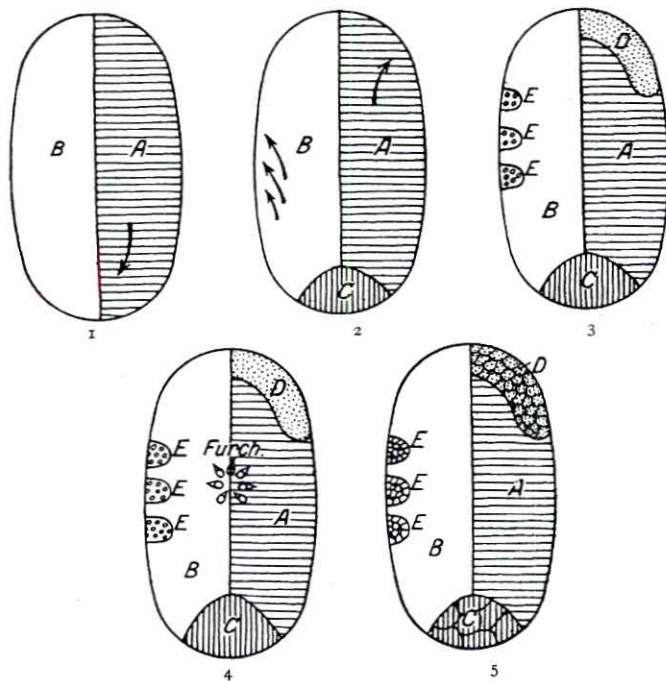
TABLE 1

PERCENTAGE OF GERMAN PUBLICATIONS IN THE REFERENCE LISTS OF E.B. WILSON'S "CELL"[1]

Chapter headings (of first edition)	n[2]	%[3]	Chapter[4]	n	%
I. General Sketch of the Cell	22	77 (76)	I	83	46 (45)
II. Cell-Division	20	80 (88)	II	62	39 (35)
III. The Germ-Cells	16	87.5	IV	80	45 (44)
IV. Fertilization of the Ovum	20	65	V	64	42 (44)
V. Reduction of the Chromosomes Oögenesis and Spermatogenesis	12	83	VI	46	37 (38)
VI. Some Problems of Cell-Organization	15	65 (54.5)	IX	78	41 (39)
VII. Some Aspects of Cell-Chemistry and Cell-Physiology	20	75	VIII	52	54 (55)
VIII. Cell-Division and Development	16	50	XIII	71	38 (36)
IX. Theories of Inheritance and Development	20	80	XIV	131	64 (61)
	161	74		667	47

[1] The title was "The Cell in Development and Inheritance" in 1896, and "The Cell in Development and Heredity" in 1925 (printing "with corrections" 1928). [2] Total of publications in the references list of the respective chapter. [3] Percentage of publications in the German language and by German authors in foreign languages. Figures in brackets: Percentage after elimination of publications cross-referenced to other chapters (Wilson gives the full title only with one chapter and refers to that chapter when listing the publication with other chapters). [4] The 3d edition had a larger number of chapters but those selected here correspond in their scope fairly well to the chapters of the first edition.

might well reflect such a bias. Therefore, some impartial testimony to the contrary should be welcome. For the pioneering days late in the 19th century, this testimony can indeed be provided with exceptional clarity. One simply needs to scan the references in the first edition of E.B.Wilson's "Cell" and compare them with those in the third (and last) edition (Table 1). In the first edition, German titles (either in the German language or by German authors writing in English or French) account for about three-quarters of the quotations in the whole book, with the individual chapters scoring between 65% and 87.5%, except for the chapter on *Cell-Division and Development* where the German quota reaches a meagre 50%. Even with some deductions granted on account of Wilson's known affinity to German culture, this can only mean that the German influence on incipient developental biology was paramount.

One-third of a century later, by the last printing of Wilson's third edition (1928), matters had changed. The overall frequency of German titles was reduced to 47% of the – much more numerous – quotations in the book; a prevalence persisted only in the closing chapter XIV (now named *Development and Heredity*), and to a lesser degree in the chapter on *Some Aspects of Cell-Chemistry and Cell-Physiology*. In the former chapter (Table 2), the percentage of German authors declined from decade to

decade; the increase after 1911 is entirely due to the abundant contributions by the Spemann school and Curt Herbst (see footnote 3 of Table 2). The trend becomes even clearer in the new chapters added to the third edition (not listed in the tables). The *Introduction* chapter of 1928 carries 41 papers and books in German (63% of the total), but of these not less than 32 (i.e. three quarters) were published before 1900, so that these quotations actually reflect the bygone pioneering days of developmental biology and the relative decline of the German influence thereafter. In the other added chapters, the German contributions ranged from 31% to 37%. The lowest quotas occured with the most modern topics (*Chromosomes and Sex* 31%, *Morphological Problems of the Chromosomes* 33%, *Heredity and Chromosomes* 31%), showing that these disciplines lagged behind in Germany.

Among the causes for this (relative) decline, the first world war and in its aftermath in Germany play only a subordinate role. The ascent of American science, which accounts for most of the difference evident in the Tables, actually came to be felt long before that war, and in 1912 provided a strong argument for founding the Institute for Biology of the Kaiser-Wilhelm-Gesellschaft (now Max-Planck-Society). This indeed became the cradle of some outstanding achievements until soon after the Second World War (Spemann, Warburg, Kühn, Butenandt, Beermann) but on the

TABLE 2

REFERENCES IN THE CLOSING CHAPTERS (IX AND XIV, RESPECTIVELY, IN TABLE 1) OF THE FIRST AND THIRD EDITIONS OF E.B. WILSON'S "CELL"

Time bracket of references	1896		1925/28	
	% German[1]	Total n	% German	Total n
until 1900	80	20	77	41
1901-1910	–	–	53.5	43 [2]
1911 ff.	–	–	61.5	39 [2],[3]

[1] For definition, see Table 1. [2] For each period, a series of reviews by D.Barfurth is listed as a single publication (contrary to Table 1). [3] Of the total of 24 German publications, 11 are from Spemann and his school, 10 from Curt Herbst and 3 from Waldemar Schleip's student Aloys Penners.

whole the contributions of German authors to the progress of developmental biology and especially to the field of morphogenesis were waning. Whoever should be inclined to mourn this might find some comfort in knowing that much of the concurrent American success had its distant roots in Germany, by way of personal ties between leading German and American developmental biologists of the first generation, and later on by the work of refugees driven to the USA by the political disasters of German history, disasters from which developmental biology in this country seems to have recovered only in recent years.

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