

# From the Aristotelian soul to genetic and epigenetic information: the evolution of the modern concepts in developmental biology at the turn of the century

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Creature made by the hands of God, animated image of the Eternal, or mere product of a soulless nature, just a physico-chemical system – what is man, what are living beings? These questions implicitly were driving forces when the occidental urge for knowledge turned to the mystery of development. The change from religious preconceptions and philosophical considerations to modern scientific concepts took place around the turn of the century and culminated in the recognition of internal (*genetic*) information as an essential principle governing living beings.

## Are living beings machines?

When the educated laity of the 17th and 18th centuries, devoted to *rationalism*, began to abandon the hitherto prevailing Christian-Scholastic philosophy and creed, the animate beings of the living world were more and more transformed into self-motive machines comparable to the admirable astronomic clocks being built by the contemporary artisans. This turn in the view of living beings was prepared by philosophers such as Descartes and Leibniz, and catalyzed by a spiritual uprising which brought forth the modern natural sciences. When in physics new branches such as the study of electricity, optics and thermodynamics came into bloom, the term *mechanical* adopted more and more the meaning of *physical*, and the term *physical*, supplemented by the appendix *chemical*, became almost synonymous with *natural*.

As Klaus Sander (1991a) in his essays "Landmarks in Developmental Biology" pointed out, the term "*Mechanik*" in "*Wilhelm Roux's Archiv für Entwicklungsmechanik*" stands for 'natural causation'. Nevertheless, much thinking in terms of *mechanical engineers and artisans* was left. Thus, August

Weismann (1892) envisioned a complicated machine that splits up the hereditary substance, presumed to be embodied in the just discovered chromosomes, by unequal mitoses. The machinery was supposed to allow organ and tissue-specific determinants to be allotted to the respective parts of the developing body in a predetermined, rigid order.

It was indeed a landmark in Developmental Biology when the young Hans Driesch, one of the first to start experimenting on embryos (in 1891/92), noticed a surprising result: "I shook the germs [of the sea-urchin] rather violently during their two-cell stage, and I succeeded ...in separating the two blastomeres from one another...But things turned out as they were bound to do and not as I had expected; there was a typically *whole* blastula in my dish next morning, differing only in its small size from a normal one; and this *small but whole* gastrula was followed by a whole and typical small pluteus-larva" (Driesch, 1907, p.61). Later he obtained not only one larva but twins and, by shaking later stages, several dwarf larvae from one and the same egg.

Driesch's conclusion, based also on the phenomenon of regeneration, was: *Living beings are not machines*, for no machine divided into parts will give rise to several whole machines, each of which replaces the missing parts by self-generation. Underestimating the intelligence and imaginativeness of future generations of engineers, he also maintained that "in principle no machine produced by chemical and physical means can be contrived as the basis of the events observed" (Driesch, 1899, p.99) [Self-replicating machines, chemical and mechanical, do exist nowadays, at least on the drawing-board. For instance: Rebek, 1994]

In teaching students, recent lecturers instantly have at hand a seemingly simple explanation of why isolated daughter cells or

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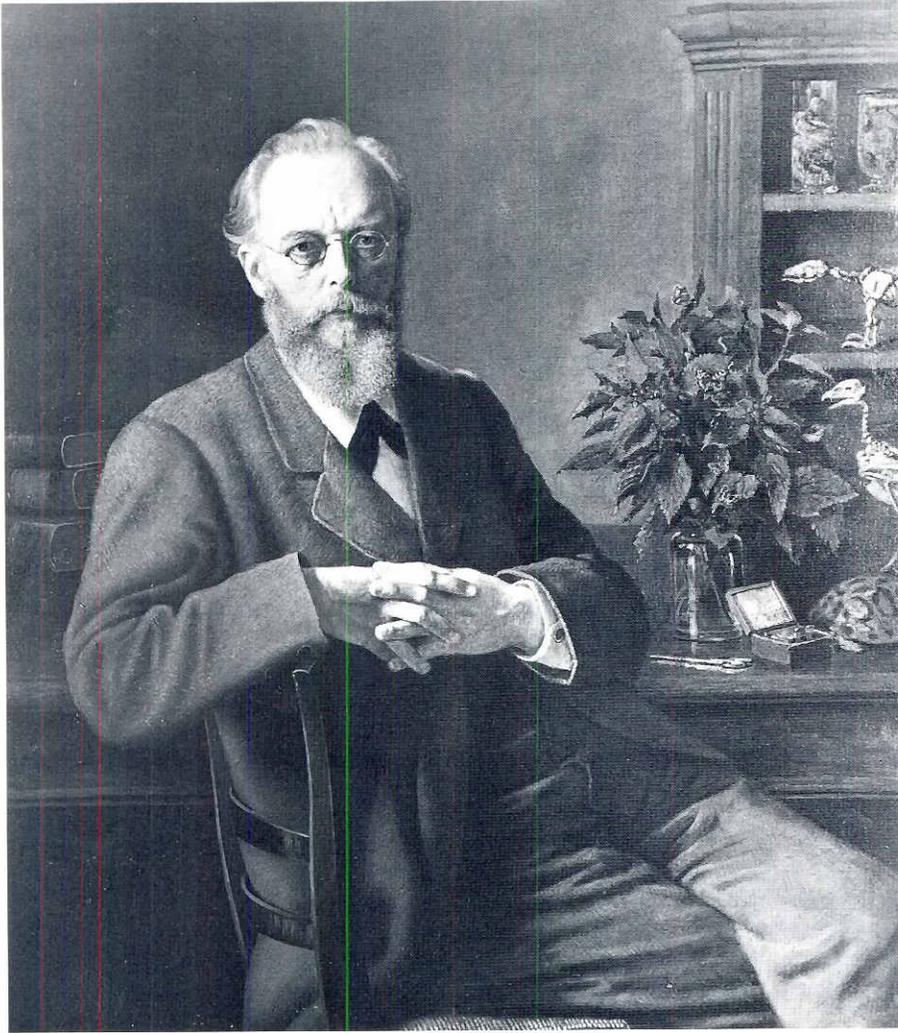


Fig. 1. August Weismann (1834-1914) (oil painting). Photograph courtesy of Prof. Klaus Sander.

pieces of a Hydra are capable of doing the same as the fertilized egg: A complete development out of parts is possible because each cell is endowed with the whole genetic information.

Driesch, by contrast, took refuge with Aristotle and his term *entelechy*. Why?

### The dawn of "information" took place only in the second half of our century

At the turn of the century, careful investigations carried out predominantly in the laboratories of German scientists provided growing evidence that chromosomes are the material carriers of inheritance. Walter Flemming in Prague and Kiel, Eduard Strasburger in Bonn, Richard Hertwig in Munich, Oskar Hertwig in Berlin, and in particular Theodor Boveri in Würzburg identified the main carriers of inheritance.

But what was a chromosome in 1891 and at the turn of the century?

It was an unknown molecular complex, presumably a container of ferment-like activities which might interact with soluble

compounds in the cytoplasm. Jacques Loeb (USA) considered the nucleus as centre of oxidation in the cell. Hans Driesch, like others, ascribed a fermentative function in the release of cascades of physico-chemical reactions to the nucleus. "We view the nucleus as a mixture of ferment-like compounds..." (Driesch, 1894, p.88). However, ferments of those days were not yet the enzymes of our days, able to 'recognize' substrates and to 'direct' reactions by 'selecting' a distinct reaction out of several thermodynamically possible ones.

To understand the dawning of an imminent, silent revolution in science we should be aware that "information" and related terms, which are now among the most often used terms in Biology, were introduced in science only in the second half of our century. Today's biologists can hardly imagine a *Biology without (genetic) "information", without (genetic) "code", without "transcription" and "translation", without "messenger molecules", "signals", "receptors", "signal transmission and transduction", without antibodies that are able to "recognize" antigens, without "control", "regulation" and "data processing"*.

Before the turn of the century there were some speculations which sought to compare inheritance with memory. As early as 1870, the physiologist Ewald Hering, known for his theories on colour vision, envisioned heredity as a kind of remembrance of all that has happened to the species in the continuity of generations. Yet, the theory was proposed to account for the assumed inheritance of acquired characters. When August Weismann (1834-1914) refuted this long-

debated notion, equating heredity with memory also appeared to be obsolete.

In the previous centuries and decades it was often the best biologists, such as William Harvey (1578-1657), Georges Louis Leclerc Buffon (1707-1788), Caspar Friedrich Wolff (1733-1794), Carl Ernst von Baer (1792-1876), Johannes Müller (1801-1858), and Claude Bernard (1813-1876), who felt unable to share the common reductionistic view that all biological phenomena could be deduced entirely from (the then known) physical laws, and who were inclined to go along with vitalistic views. Their patron was Aristotle.

### The Aristotelian soul: form, *energeia*, *entelecheia* and genetic information

No personality has influenced occidental thinking more than the ancient Greek philosopher and universal scientist Aristoteles, Aristotle (384-322 aC). An enthusiastic zoologist, he was the first to describe the development of the chick in his treatise "On the generation of animals". Essential theoretical exposi-

tions on development are also found in his writings on *Metaphysica* ('Beyond physical sciences', 'Beyond nature') and *De anima* ('On the soul').

In studying the development of the chicken, Aristotle saw an initially formless white and yellow *matter*, in Latin *materia*, the unstructured stuff contributed by the *mater*= mother. This matter undergoes "*morphogenesis*" (his term!). In the midst of this form-becoming mass a "jumping point", the beating heart, demonstrates that some kind of power is exerting motion.

What is the forming principle? It is *energeia* ('energy'), from *en*= in, inherent, and *ergon*= work. The Greek term *ergon* has a double sense similar to the English term 'work' or the German term *Arbeit*, denoting on the one hand power exerted by a moving agency or a human being, and on the other hand the product of an artist. As a synonym of *energeia* Aristotle even more often used the term *entelecheia* from *en*= 'inherent', *telos*= 'end, goal, aim', and *echein*= 'to have'. Development is governed by a principle which bears the end in itself and shapes structureless matter, striving for a species-specific form.

*Energeia* or *entelecheia* are likewise the efficient and final cause of a living body. Moreover, *entelecheia* also denotes the finished work. In the language of the Platonic-Aristotelian-Scholastic philosophy, matter is mere *dynamis*= potentiality, the finished form is *energeia/entelecheia*= actuality, is actual existence, is synthesis of matter and idea.

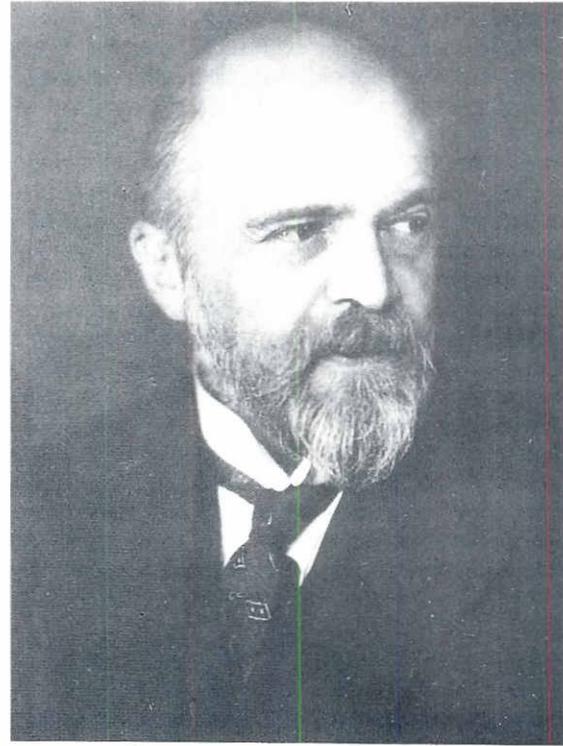
To reach a defined species-specific end, the forming principle must have a "*pre-existing idea*" of the final outcome. "Natural production is like artificial; the seed operates like those who work by art". And "artistic production presupposes the presence of form of the product in the soul of the artist." (*Metaphysica* II, ed. by W.D. Ross, 1924, Z.7. 1032-Z.9.1034). Hence, it follows that the final *energeia* or *entelecheia* in development is *the soul*.

In the generation of man, it is – thus Aristotle – the female parent who contributes the vehicle of the specific form. The matter capable of adopting this specific form is found in the surplus blood. It is the male parent whose sperm carries the soul, which will impose the specific form on the female matter. (In a female child the specific nature of the male parent is reproduced but is embarrassed by the inferior matter with which it has to cope!).

Thus, the soul is the means to all vital power and life. The living body acquires all its attributes by virtue of soul. However, the soul displays gradation. Its lowest faculty is the vegetative= nutritive power, higher faculties are sensations, appetitive, imaginative and intellectual powers.

Aristotle in *De anima* literally: "The vegetative soul belongs to other living things as well as to man, being the first and most widely distributed faculty, in virtue of which all things possess life". "Now the soul is cause and origin of the body." "...for the soul is the cause of animate bodies being in itself the origin of motion, as final cause". "Qualitative change, also, and growth are due to soul". "...nothing devoid of soul has sensation. The same holds of growth and decay". "The nutritive faculty of the soul being the same as the reproductive".

"It [the soul] causes the production...of another individual like it. Its essential nature already exists, ...it only maintains its existence. Hence the ...principle of the soul is the power to preserve in existence that which possesses it in so far as it is a definite individual".



*Hans Driesch*

Fig. 2. Hans Driesch (1867-1941). Photograph courtesy of Prof. Klaus Sander.

"The primary soul is that which is capable of reproducing the species" (*De anima*, 416 b1-416 b27).

### The entelechy of the vitalist - Hans Driesch

"Entelechy has ruled the individual morphogenesis of the generation which is regarded as the starting point for inheritance, and will rule also the morphogenesis of the generation which is to follow" (Driesch 1908, p.227-228). "Entelechy thus proves to be also that which may be said to lie at the very root of inheritance." (Driesch, 1907, p. 226).

Driesch emphasizes again and again that his entelechy is not a vitalistic "force"; instead he defines it as "intensive manifoldness" and associates terms such as "order" and "knowledge" with it. Entelechy selects between all the thermodynamically possible reactions, thus creating "extensive manifoldness", that is ordered complexity.

However, in hindsight Driesch made several severe mistakes that made his entelechy unacceptable:

(1) Entelechy was thought to be immaterial and not mediated by a physical carrier. One might sophisticatedly discuss at length whether information as such, or likewise negentropy, is material, and what "material" is at all. (The textbooks in physical sciences do not hesitate to classify apparently mass-less phenomena such as magnetic fields or electromagnetic waves as immaterial.) Whatever the outcome, it is simply a fact that genetic information is carried by macromolecules.

(2) Though entelechy does not reside in space, it acts in and into space. And although Driesch emphasizes that entelechy is not a force, it is able to direct material events by "suspending" physical forces. With respect to the laws of energetics, he says: "Entelechy, as endowed with the faculty of enlarging the amount of diversity..." And: "The work of the "demons" of Maxwell is here regarded as actually accomplished" (Driesch, 1908, p.225.). Like Maxwell himself, Driesch did not realize that these demons would have to spend or consume some energy to obtain information on the kinetic energies of the molecules. Apparently, Driesch did not convince any of the renowned contemporary physicists.

(3) Driesch's entelechy grew to a universal entity just like the soul of Aristotle. It governs life in all its qualities. In its manifestation as "psychoïd", entelechy took over all the various functions of the Aristotelian soul.

Like the soul of Aristotle, the entelechy of Hans Driesch became a source of universal information capable of governing all that could not be explained in the terms of contemporary science. In development, entelechy had to cover all kinds of endogenous information, regardless of the source of the respective information and its functional context (see below "positional information").

It was Biology at the turn of the century, as it arose in Germany and the USA, which began to subdivide and to resolve the complex of sources of information at work in development.

### The three internal sources of information

We now have to distinguish three sources of endogenous information, (1) the genetic information encoded in the DNA of the nucleus and the mitochondria, (2) maternal cytoplasmic information which is directly (always?) derived from genetic information, (3) epigenetic information acquired by the interaction of the cells. At the latter, supracellular level of organization genetic information is only indirectly involved, as it provides the possibility to produce signal molecules, receptors, signal transducing systems and ultimately transcription factors.

#### Genetic information

A few years after Driesch's epochal experiment, Theodor Boveri (1904a) was able to deduce the Mendelian rules from the behaviour of the chromosomes in meiosis. He predicted the coupling of the genes in groups according to the number of chromosomes in the haploid state of a germ cell, a prediction later verified by a friend of Driesch, Thomas Hunt Morgan (USA). But it was only in the second half of our century when the primary 'semantics' of the genetic code, its role in determining the sequence of bases in the various types of RNA and, hence, of the amino acids in polypeptides, was revealed.

#### The cytoplasmic determinants (maternal information)

From the early beginning of experimental embryology attention was directed towards intimate cytoplasmic inhomogeneities that would endow the cells receiving them with differential dispositions for particular developmental pathways. Careful observations and subtle surgical interventions by Wilhelm Roux, Theodor Boveri, Edmund B. Wilson and Thomas Hunt Morgan led to the view that the morphogenetic potencies are not uniformly distributed in the cleaving egg. Wilhelm Roux,

one of the first to recognize the suitability of the mitotic apparatus to enable an equal distribution of the hereditary material, also discussed the possibility of unequal mitoses as a means by which 'organ-forming territories' might be established (Sander 1991b, and references therein). The hypothesis of differential mitoses had been a central notion in the innovative but highly speculative theories of August Weismann (Sander, 1991, and references therein).

The clue to the existence of two separate sources of developmental potencies was found in studies of the utmost minuteness carried out in the USA and Germany.

(1) In the school of Edmund B. Wilson careful and patient observations of spiralian embryos not only led to the establishment of defined "cell lineages" but also to the singular observation that in the cleaving egg of the marine mollusc *Dentalium* the vegetal lobe (then "yolk-sac") does not contain a nucleus. The removal of this lobe nevertheless led to larvae lacking the mesenchyme (E.B. Wilson, 1896, and references therein).

(2) By observing dispermic eggs, and later by centrifuging uncleaved eggs, Theodor Boveri (1904b, 1910) showed that in the nematode *Parascaris* graded cytoplasmic qualities determine whether a cell enters the pathway to becoming a somatic cell (which exhibits the phenomenon of chromatin diminution) or a primordial germ cell (which retains the complete chromatin).

It also was Theodor Boveri (1910b) who introduced the gradient hypothesis (Also: Sander, 1993, and references therein). As early as 1902 Boveri had envisioned "that the simple differentiation of the cytoplasm serves to set in motion the machine whose essential and probably most complex mechanism resides in the nucleus."

When after the severe collapse during and between the two world wars German Developmental Biology began to revive, the idea of gradients was resumed (for instance: Sander, 1976, and references therein) and found its final verification in the demonstration of the bicoid gradient by Christiane Nüsslein-Volhard and her coworkers. The bicoid products mutually linked genetic information with the cytoplasmic determinants: On the one hand, the bicoid determinant is derived from the maternal bicoid selector gene as its mRNA copy, on the other hand its translational product, the BICOID protein, is a transcription factor controlling sets of subordinate, 'zygotic' genes in the developing germ. Since this important discovery was published (e.g. Nüsslein-Volhard *et al.*, 1987) the number of identified cytoplasmic determinants derived from maternal genes is growing almost monthly.

#### Acquisition of new information by cell interactions: positional information and induction in multicellular systems

The third level at which information governs pattern formation, cellular differentiation, morphogenesis and the whole complex of self-organization, is the level of cell interactions or cell society. For the sake of simplicity, the paradigm of *positional information* shall stand for this level (which, however, also comprises chemotaxis, transmission of non-spatial information by mitogenic factors, hormones and nervous conduction).

It was once more Hans Driesch who first recognized the phenomenon explicitly when he wrote his *Fundamentalsatz* (fundamental statement, theorem): "The prospective significance of each blastomere [the fate of a cell] is a function of its position in



*W. Roux*

Fig. 3. Wilhelm Roux (1850-1924). Photograph courtesy of Prof. Klaus Sander.

the whole" (Driesch, 1894). This is not his only statement on this topic. A whole booklet was devoted to this phenomenon (Driesch, 1899). Only a few expositions, written in English by himself in "Science and Philosophy of the Organism: Gifford Lectures 1907" (published in 1908) may be quoted:

p. 101: "...that each single elementary process or development not only has its *specification*, but also has its specific and typical place in the whole - its locality".

p. 127: In the hydroid *Tubularia* "you may cut the stem at whatever level you like: a certain length of the stem will always restore the new head by the co-operation of its part. As the point of section is of course absolutely at your choice, it is clear ... that the *prospective value* of each part of the restoring stem is a "*function of its position*", that it varies with its distance from the end of the stem."... "But also the second point...can be demonstrated in

*Tubularia*: the dependence of the fate of every element on the actual size of the system."

When Lewis Wolpert independently revived the idea of positional information he used a remarkably similar terminology: "specification", "positional value" instead of "prospective value".

Yet, there are also differences between the concepts of Wolpert and Driesch. While Wolpert derives positional information from gradients, Driesch in his early writings developed a concept of inductive interactions. Years before Spemann, Driesch attributed positional effects to the following list of factors:

1. Mass-induction [meaning cytoplasmic factors]
2. Induction by tension and pressure
3. Contact induction
4. Chemical induction
5. Induction by chemical orientation [i.e. chemotaxis]
6. External induction.

But, instead of starting the analysis of the proposed factors, Driesch deviated into the sphere of metaphysics, assigning the final control over all physico-chemical events to his entelechy. By doing so, he discredited the whole topic.

By contrast, in the writings of Wolpert, there was never a doubt that he was speaking of natural, epigenetic phenomena which can be understood and analyzed by physico-chemical means, supported by computer simulations. Therefore, his type of approach was fruitful and will be continued.

#### **Different personalities may contribute to common scientific concepts**

In the realm of Biology, we cannot point to one single genius who had developed the concepts of today's Developmental Biology. The emerging concepts are the resultant of common and diverging thoughts expressed by personalities so different as Hans Driesch and Theodor Boveri.

Here the colourful eloquent cosmopolitan, gifted with unlimited self-confidence and even an attitude of arrogance, rather cursory in his observations and in his sketches, but also endowed with a highly imaginative, ingenious spirit. His soaring mind, however, drove him into that sphere which in the German academic world and cultural tradition was always valued more highly than natural sciences: philosophy.

On the other hand, his counterpart, the 'provincial' zoologist, shy, scrupulous, perfectionistic, extremely careful in his observations and experiments, documenting them with superb, exact drawings, but also endowed with a highly astute spirit.

Science can integrate all personalities devoted to the search for truth, irrespective of their peculiar characters and their nationalities.

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