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THE REDUCTION OF CLASSICAL EXPERIMENTAL EMBRYOLOGY TO MOLECULAR DEVELOPMENTAL BIOLOGY

A Tale of Three Sciences

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I ATTEMPT TO CHARACTERIZE the relationship of classical experimental embryology (CEE) and molecular developmental biology and compare it to the much-discussed case of classical genetics. These sciences are treated here as discovery practices rather than as definitive forms of knowledge. I first show that CEE had some causal knowledge and hence was able to answer specific why-questions. A paradigm was provided by the case of eye induction, perhaps CEE's greatest success. The case of the famous Spemann-Mangold organizer is more difficult. I argue that before the advent of molecular biology, knowledge of its causal role in development was very limited. As a result, there was no functional definition of the concept of organizer. I argue that, like the classical gene concept, it is best viewed as an operational concept. This means that an account of reduction such as Kim's functional reduction, which is still a mainstay in scientific metaphysics, cannot work in these cases. Nonetheless, again like in the classical gene case, the operational concepts of CEE played an important heuristic role in the discovery of molecules involved in morphogenesis and cell differentiation. This was made possible by what I call inter-level investigative practices. These are practices that combine experimental manipulations targeting two (or more) different levels. I conclude that the two sciences are more closely related via their experimental practices than by any inter-level explanatory relations.

1. INTRODUCTION

Debates about reduction, mechanism, and physicalism have accompanied developmental biology since its historical beginnings in the nineteenth

century (Weber 2022). While some biologists and philosophers thought that development can only be explained by postulating immaterial vital forces, the recent identification of numerous molecular mechanisms involved in the control of cell differentiation and growth seems to support some form of reductionism or another (Rosenberg 2006). Indeed, it is a recurrent feature of modern biology that a once-autonomous discipline with its own concepts, theories, investigative techniques, and so on becomes absorbed into the molecular mainstream and starts to use molecular techniques to identify and characterize molecules that play a role in the phenomena they are interested in.[1] Scientists and philosophers alike have given in to the temptation of describing this trend toward molecularization in terms of reduction and seeking parallels to other sciences, in particular physics. According to the standard view, reduction in physics consists of a derivation of the laws of the theory to be reduced from a fundamental theory.[2] Attempts by philosophers of biology to apply this model to the case of classical genetics and molecular biology (Schaffner 1969) eventually led to a consensus according to which this is not possible because the necessary bridge principles connecting the terms of the two theories do not exist (Hull 1974; Rosenberg 1985). In a nutshell, this is because central genetic concepts such as dominance can be realized by many different molecular mechanisms, making it impossible to find a molecular concept that corresponds to it exactly, which is what reduction traditionally conceived would require.[3] Thus, physics turned out to be a poor model for reduction in biology.

Since then, philosophers of biology, as well as some physicalistically oriented philosophers of mind, have shifted attention from theory reduction to reductive explanation, asking not if and how some central theory might have been reduced to a fundamental theory but instead focusing on cases where some specific biological phenomenon such as the brain's ability to perform a cognitive task or muscle tissue's ability to contract has been explained by identifying a molecular mechanism, or more generally a mechanism at a lower level (Wimsatt 1976; Weber 2005; Kim 2007; Craver 2007; Kaiser 2015; Bechtel 2006).

While these accounts are compelling at least for some cases, they mainly concern what is known as *inter-level reduction* (i.e., the question of how the properties of complex systems can be explained by the properties of the parts). This raises the question if cases of *diachronic* reduction (Nickles 1973), such as the historical transition of a body of knowledge like classical genetics to molecular biology, can also be analyzed in terms of reductive explanation.

Before we can answer this question, we must first know what should be reduced to what. In the much-discussed case of classical genetics and molecular biology, it turned out to be difficult to even answer this first question. Inspired by physics, we might look first for an explanatory theory or set of principles of classical genetics and then for a fundamental theory that explains it. The most obvious candidate for such an explanatory theory is the account of various inheritance patterns that classical geneticists offered. Here is an example: the fact that two genes are located on different chromosomes explains why they assort independently in Mendelian crosses, while linkage in genetic crosses is explained by the genes being located close together and on the same chromosome. Occasional failure of linkage is explained by the chromosomes sometimes exchanging parts during their alignment in meiosis, which can be observed under a light microscope. Thus, the pairing and separation of chromosomes during meiosis explains the regularities of gene transmission discovered by classical geneticists. Some philosophers, most notably Kitcher (1984), have argued that this explanation, which remains strictly at the cytological level, is better than any molecular account, which would provide only "gory details."

Waters (2008) argues that this view is mistaken in several ways: First, Kitcher was unduly pessimistic about molecular biology's potential to discover the molecular mechanisms behind meiosis. Second, these molecular accounts do improve over the purely cytological accounts of these processes. However, seeking and finding these better explanations is not the development that has transformed genetics. In fact, it is just one among many achievements, and a more peripheral one for that matter. What transformed biology is what Waters calls a new basic theory that contains a new understanding of what genes are as well as explanations of how DNA is replicated and how proteins are made. However, this basic theory is unlike the fundamental theories of physics in that it is not able to explain all the facts in its domain. Instead, the basic theory is best viewed as being part of a new toolbox that still contains methods from classical genetics and that is being used by biologists to learn more and more about the functions of various parts of the organism.[4] This is what the molecular revolution in biology is all about. For example, a mutant of the nematode worm *C. elegans* named *unc*-70 (originally discovered by using methods from classical genetics) allowed biologists to unravel the function of the protein β-spectrin in the development of the nervous system.[5]

Waters's account shows that an exclusive focus on theories and explanations has led philosophers to misconstrue the relationship between classical

genetics and molecular biology. Close attention to the practices of discovery used in these disciplines has led to a more adequate characterization of how these sciences are related.

In this chapter, I would like to extend this discussion to an area that has received much less attention from philosophers than classical genetics, namely classical experimental embryology (henceforward CEE) from the early twentieth century and its relationship to molecular developmental biology, a field that has seen major advances in recent decades. CEE was initially mainly practiced on amphibian embryos, which are easy to manipulate and have the advantage of developing in isolation. One of CEE's chief interests concerned the phenomenon of induction. This designates a process during which embryonic tissue that would by default follow some specific developmental path receives a signal from another tissue that changes its fate (e.g., from normal epidermis to lens tissue). It has been suggested that CEE did not provide any explanations of such phenomena; it merely described them, while genuine explanations had to await the discovery of the first molecules that bring about these changes, for example, so-called homeobox genes and their products (Rosenberg 1997). In this view, all that CEE contributed was merely a set of explananda and no explanantia nor anything else.

I will draw a somewhat different picture of how CEE and molecular developmental biology are related. By examining the classic examples of eye induction and Spemann's organizer, I will show that CEE did have some causal and hence explanatory knowledge. Perhaps the clearest example is provided by the case of eye induction. However, I will also show in section 2 that a particularly influential finding from CEE, the Spemann-Mangold experiment (including subsequent refinements thereof), provided at most a very weak kind of causal knowledge.

I will show in section 3 that this makes it difficult to assimilate this case into an account of explanatory reduction such as Kim's (2007). I will argue that, much like the classical concept of the gene, the organizer is better understood as an operational concept with enormous heuristic value rather than a functional concept with mainly explanatory value. Thus, CEE provided more than just explananda (phenomena to be explained) and perhaps some modest causal knowledge. It provided also investigative techniques and operational concepts that served as important tools for identifying molecules. In section 4, I will propose that CEE became part of what I call an *inter-level investigative practice* in which certain classical concepts functioned as re-

search tools. In section 5, I will draw together the parallels and differences to the case of classical genetics.

Without further ado, I will now take a look at CEE by paying special attention to the question of what kind of knowledge this science had.

2. THE KNOWLEDGE OF CLASSICAL EXPERIMENTAL EMBRYOLOGY

The origins of CEE are often identified with the German tradition of *Entwicklungsmechanik* that emerged mid-nineteenth century. Wilhelm Roux is widely seen as the founder of this tradition, but as Maienschein (1991) shows, there was increasing interest in individual development and in experimental methods in various research centers at that time, not only in Germany. Nonetheless, Roux's experiments with frog embryos were clearly influential. Like many embryologists at that time, Roux was interested in the causes of cell differentiation in the first cleavage divisions of amphibian embryos. The initial debate was about the question of whether these causes are internal or external to the embryo. An example of an external factor would be gravity, but unlike in plants it seemed to have no effect on animal development. Roux's preferred theory was one of "self-differentiation" according to which inner causes determined the first cells toward different fates. One of his most influential experiments involved the destruction of one of the cells of a two-cell frog embryo by punctuation. He found that the surviving cell will typically form a partial embryo and took this to support his "mosaic theory" of development according to which the different parts of the embryo develop independently (Roux 1888).

Another influential investigation was carried out by Hans Driesch on sea urchin embryos. Driesch found that each one of the cells of a sea urchin up to the eight-cell stage was able to form a whole (if smaller) pluteus larva (Driesch 1892). He interpreted this phenomenon in terms of regulation.[6] In his view, embryonic cells were internally determined to the same fate, but they were able to change their differentiation state as a function of their surroundings. He introduced a distinction between the prospective fate (*prospektive Bedeutung*) and prospective potency (*prospektive Potenz*), where the former is a function of an embryonic part's location within the whole embryo. A region with constant prospective potency forms a harmonic-equipotential system (*harmonisch-äquipotenzielles System*). Driesch later

used this phenomenon in his arguments for vitalism (Weber 1999), but at that time, he was still an orthodox *Entwicklungsmechanist*. What his findings showed was that the fate of an embryonic cell was not predetermined by some rigid program. Rather, the cells take cues from the surrounding cells when they divide and adapt their differentiation state according to their position in the embryo. A rather spectacular example is provided by the two blastomeres of the two-cell sea urchin embryo: when they are attached to each other, each of these cells will form a half embryo. When detached, each one can form a whole embryo.

One of the most intensely studied phenomena—and perhaps CEE's most important explanatory success—was the induction of the lens by the neural tissue that will later become the brain. In 1901, Hans Spemann published a study where he destroyed the eye rudiment on one side of *Triturus* (Northern European newt) embryos with a hot needle and observed that the lens failed to form on that side where he had intervened (Spemann 1901). He thus concluded that lens formation in the epidermis was caused by the optic vesicle underlying the epidermis, a process that he termed "induction." This conclusion was also supported by experiments done by Warren H. Lewis (1904) showing that optic vesicles transplanted to the flank of frog embryos caused the appearance of a complete lens. Induction became one of the guiding concepts in CEE, and embryologists interpreted most of their results in these terms (Saha 1991). In other words, it served as some sort of a paradigm, perhaps even in Kuhn's (1970) sense. The simple induction account was later refined considerably in Spemann's and in other laboratories, telling a more nuanced causal story. However, the lens induction results as well as their theoretical interpretation turned out to be one of the most lasting contributions of CEE, and I will shortly provide reasons why it may be one of its greatest explanatory achievements.

Another highly influential finding was the famous Spemann-Mangold experiment published in 1924.[7] Spemann's PhD student Hilde Mangold cut a small piece of tissue from the upper blastopore lip (the place where invagination begins in the process of gastrulation) from *Triturus cristatus* embryos and transplanted it to the ventral side of another embryo of the closely related species *Triturus taeniatus*. She found that the transplant induced a secondary embryo on the embryo's ventral side. Spemann and Mangold thus introduced the idea of an "organizer," an embryonic tissue capable of changing the fate of recipient epidermis cells and organizing them into forming an entire new body axis as well as several rudimentary organs such as the

neural tube and the ear vesicles. *Triturus cristatus* and *taeniatus* were deliberately chosen because these two species differ in pigmentation. This allowed Spemann and Mangold to show that the secondary embryo was mostly built from tissue of the recipient and that the donor tissue only gave rise to the notochord. Thus, it wasn't just the transplant growing into a secondary embryo; the transplant clearly did something to the recipient tissue to change its fate into forming a new body axis (instead of just the ventral epidermis that it would have formed without the intervention).

The Spemann organizer soon became the holy grail of CEE, not least because it held promise to isolate the substances that mediated the organizing effect (an approach not favored by Spemann, and indeed it failed, but not for the reasons that motivated Spemann's doubts; see Hamburger 1988). However, trouble with Spemann's organizer concept soon arose when it was shown that there are many so-called "heterologous inducers," substances other than a newt blastopore lip that had a very similar effect when inserted into the ventral side of a newt embryo. Such inducers included boiled organizer tissue, various fractions from such tissues, fatty acids and sterols, and even nonphysiological substances such as sand particles or methylene blue. In the axolotl, even a saline solution worked as an "organizer." These findings called the whole organizer concept into question because they suggested that the organizing power is really in the receptor tissue and that it was merely triggered by the intervention. Spemann always emphasized that the receptor tissue needs to be *competent* to be induced. Nonetheless, the general perception was that heterologous inducers were a "funeral march" for the organizer theory or even that "Spemann's organizer set developmental biology back by 50 years" (De Robertis 2006). Indeed, the exact interpretation of the organizer findings was controversial until very recently.

These problems notwithstanding, it would be a mistake to see CEE as a failure. The science clearly had explanatory achievements. At least it was able to answer some of the questions that its practitioners raised. In order to analyze what kind of knowledge CEE produced, I would like to come back to the paradigmatic case of lens induction. Here are some of the questions raised by Hans Spemann in his 1936 book:

> [W]ie kommt dieses auffallende zeitliche und räumliche Zusammenpassen der einzelnen Entwicklungsprozesse zustande? Woher kommt es, daß die Linse gerade an derjenigen Stelle der Epidermis zu wuchern beginnt, wo sie

> vom Augenbecher berührt wird, gerade zu dem Zeitpunkt, wo die Anlage der Retina sich einbuchtet? Üben beiderlei Vorgänge einen Einfluss aufeinander aus [. . .]? Oder verlaufen vielmehr beiderlei Vorgänge unabhängig voneinander, unter Selbstdifferenzierung der getrennten Anlagen, und beruht ihr genaues Zusammenpassen auf einer vorher erfolgten genauen Abstimmung der Teile aufeinander? (Spemann 1936, 26)

> [**My translation**] How does this remarkable temporal and spatial fit of the different developmental processes arise? Why does the lens start to grow in the very spot where the optical cup touches the epidermis, at the exact time when the retinal *Anlage* invaginates? Do both processes exert an influence on each other [. . .]? Or do they proceed independently of each other, under self-differentiation of the separate *Anlagen*, while their fit is based on a preexisting exact harmonization of the parts to each other?

As always when two events coincide in space and time, this could be due to a causal interaction or due to a preestablished harmony of processes that are causally isolated from each other. Spemann wondered which one it was in the case of eye development. His experiments strongly suggested that it was a causal interaction. This was an explanatory achievement: a question about causality—preestablished harmony versus interaction—was answered. By and large, this answer is still considered to be essentially correct today.[8]

Thus, in contrast to what Rosenberg (1997) claimed, CEE clearly had some causal knowledge, and this knowledge answered important why-questions like the ones about eye induction just discussed. I also believe that Driesch's findings briefly reviewed earlier told embryologists something important about developmental causality, namely that the developmental fate of cells can depend on causal interactions with other parts of the embryo. However, it must be admitted that all this causal knowledge was very rough in the sense that not many causal variables had been identified and the ones that were identified were not highly specific in the sense that they did not allow scientists to control developmental processes in a very fine-grained way.[9] Furthermore, what characterizes most of this knowledge is a certain remoteness of the causes from the effects.[10] This is particularly striking in the case of the organizer. The Spemann-Mangold experiment and its subsequent refinements merely showed that the blastopore lip (or parts of it) has the power of triggering the formation of a body axis in transplantation experiments. But what was actually observed was merely the end result

of this reprogramming of the cells in the recipient tissue. Exactly what developmental events were triggered was unknown at the time. As I will show in the following section, the initial hypothesis (neural induction) turned out to be false.[11] Finally, the implications for normal development were not clear at the time, as witnessed by the extensive controversies surrounding the iconic organizer experiment.

In its remoteness of causes and effects, the case of the organizer resembles the classical gene, which was only known to cause uniform phenotypic differences in particular genetic and environmental contexts (called the "difference principle" of classical genetics; see Waters 2008 and section 3 later in this chapter).

If this is correct, why does the Spemann-Mangold experiment still feature so prominently in developmental biology textbooks? In order to answer this question, I suggest that we should look to the case of classical genetics and the way in which biological concepts sometimes serve as investigative tools.

3. OPERATIONAL CONCEPTS AND THE FAILURE OF THE FUNCTIONAL APPROACH TO REDUCTION

Since the 1980s, molecular developmental biologists have identified hundreds of genes and gene products in various organisms that are today believed to be responsible for some of the effects observed by early experimental embryologists. Many of these gene products are transcription factors, which means that they bind selectively to DNA at specific regions and activate or block the expression of specific genes. Others are signaling molecules that regulate the proliferation or differentiation of cells. Some of these molecules are secreted by the cells making up the organizer, diffuse through the embryonic tissue, and bind to receptors on other cells, which then send a signal to the nucleus, which changes the differentiation state of these cells. There are also molecules that regulate or cause cellular movements such as the invagination of the lens placode (a thickening of the epidermis that will later form the lens). Needless to say, these processes are enormously complex. Before considering to what extent knowledge about such molecules and their interactions reduces the knowledge about induction and organizers from CEE, let us first recall what such a reduction might look like.

It is clear that a model of reduction such as Ernest Nagel's (1961) according to which reduction consists in the derivation of some laws from more

fundamental laws isn't applicable here. Even if we grant that the phenomena described by CEE can be stated in the form of laws, there is no molecular theory from which these laws can be deduced. Biological knowledge is usually not organized into theories that consist of a few basic principles that can in principle explain all the phenomena in its domain (Waters 2008).

A more promising approach to reduction is the one elaborated by Jaegwon Kim (2007) for his metaphysics of the mind, taking genetics and molecular biology as a model. According to Kim, a successful reduction proceeds as follows:

(1) Provide a functional definition of the phenomenon to be reduced, i.e., having M $=_{def}$ having some property or other P (in the reduction base domain) that exerts causal role C
(2) Identify the properties or mechanisms in the reduction base that perform C
(3) Explain how the realizers of M perform C

I will not consider the merits of this account in general; maybe there are positive examples to be found.[12] However, my contention is that such examples will concern at best cases of inter-level reductive explanation. Such cases differ considerably from putative cases of diachronic reduction, which concern the relationship between an older and a more recent body of knowledge (Nickles 1973). I suggest that Kim's account does not apply to such cases because some of the crucial scientific concepts do not admit of Kim-style functional definitions. If we consider the case of classical genetics, we will find that there was nothing like a causal role associated with the pre-molecular gene concept. Kim himself (2007, 101) suggests that the functional definition of a gene is "a mechanism that encodes and transmits genetic information." This is too broad, as there are many mechanisms that could be said to encode and transmit genetic information (Oyama 2000).[13] What is more, the notion of genetic information is notoriously unclear.

Thus, there is no such concept of the gene as Kim imagined it. There are only two things to be found in the practice of classical genetics: (A) There is what Waters (2008) calls the *difference principle*: differences in a classical gene cause uniform phenotypic differences in particular genetic and environmental contexts. As I have already argued in the last section, this is at best a remote or unstable causal link (which was nonetheless instrumentally important for identifying genes). (B) There are *operational criteria* that

were used by classical genetics in order to identify genes experimentally. Briefly, these criteria involved very elaborate crossing experiments with a variety of different mutants of an organism. To put it in a nutshell, two (recessive) mutations were considered to affect different genes if the phenotypic effects disappeared when both mutations were present in the genome, a phenomenon known as "complementation." When the phenotypic effects did not disappear, they were considered to reside in the same gene. Of course, there are lots of complications with this so-called complementation test, but these need not concern us here. What matters is that classical genetics used a combination of genetic mapping and complementation test in order to assign mutations to genes and thus were able to localize genes and their approximate boundaries on the chromosomes.

I wish to claim that neither (A) nor (B) provides a functional definition of the gene in the sense of Kim. This is easy to see in the case of (A): To be a cause of uniform phenotypic differences in particular environmental and genetic contexts is not a unique property of genes. Furthermore, there is no one-to-one relation between phenotypes and genes.

What about (B)? I claim that this is no causal role of the kind that could feature in a functional definition either. There are two reasons. First, one would expect a causal role to be something that the entity in question exerts even if no experiment is performed. But complementation is an effect that shows up only in very specific experiments. Of course, the explanation for why complementation works has something to do with the genes' physiological causal role. But that role was unknown to classical geneticists, so it couldn't have been part of an explicit functional definition. The second reason is that there are many genes for which the complementation test doesn't work, and classical geneticists knew this. There are also cases where it gives completely misleading results because there are phenomena such as interallelic complementation, different mutations that cancel or partially cancel each other's effects even when they are located on the same gene. (Note that partial complementation is always an indication that something is odd.) All these phenomena were known to classical geneticists, and they didn't consider them as severe anomalies for the gene concept.

Another way of putting my claim is by saying that classical geneticists did not have a functional definition nor any other theoretical definition of the classical gene because all they had was an operational concept. By using the notion of operational concept, I am not committing to a form of operationalism according to which the meaning of all concepts is reducible to or even

synonymous with a set of operations, as Bridgman (1927) famously suggested. I am not subscribing to a general philosophical view about meaning;[14] I only wish to commit to the following claims: First, classical genetics did not have a specification of a causal role that was necessary and sufficient for being a gene. Second, there were experimental procedures for detecting and localizing genes on chromosomes (procedures that broke down for some cases; see Weber 2005, ch. 7 for details). Thus, while the classical gene concept contained the criteria for experimentally identifying or detecting genes, it doesn't say what their causal role is in the organism's development. This doesn't mean that there was *no* theoretical knowledge about genes. For example, it was known that they are arranged linearly on the chromosomes. And of course it was known that differences in genes can cause differences at the phenotypic level (the "difference principle" according to Waters). But none of this theoretical knowledge amounts to a theoretical definition, since it was in itself insufficient for identifying genes. Thus, when I qualify the classical gene concept as "operational," what I mean is not that the concept had no theoretical content. I only mean that this content wasn't sufficient to identify genes.[15] We could say that classical genes are those entities that are arranged linearly on chromosomes, cause phenotypic differences, and are detectable by classical genetics' experimental techniques. But this is no theoretical definition; it contains an ineliminable reference to experimental techniques. Note also that there is no completed or corrected version of classical genetics that contains a functional definition. There may be a functional definition of the *molecular* gene, but that is supposed to occur only in step 2 of Kim's reduction model.

What is also important to note is that, even though there is no clean one-to-one mapping of classical and molecular genes, the operational criteria of classical genetics were extremely helpful for identifying lots of molecular genes (Weber 2004). Thus, what mattered most for the advancement of biology was not the existence of some explanatory relation between the theories or concepts of the classical and the molecular bodies of knowledge but the possibility of what I wish to call inter-level investigative practices, that is, practices that combine classical and molecular techniques. It is there that we find the most important diachronic relations, not by looking only at theories or at explanations. I will say more about this notion in section 4. But first, I wish to suggest that the case of inducers and organizers bears an important resemblance to the case of the classical gene.

Classical experimental embryologists led passionate debates as to what inducers or organizers are. They never reached a consensus (Hamburger

1988). More recently, some philosophers of biology have attempted to define the role of the Spemann organizer in abstract causal terms, arguing that it was initially conceived as a causally specific instructive cause but turned out to be merely a switch or a permissive cause (Calcott 2017; Bourrat 2019). While these analyses are conceptually illuminating, they cannot help explain why the organizer concept was and is so important in developmental biology. I would rather like to suggest that, much like the classical genes, organizers were basically *operationally* defined concepts. Evidence for this can be found in a recent review article by two contemporary biologists:

> The notion of an organizer refers to specific experiments that test the signalling ability of specific groups of cells in particular contexts. The use of the term "organizer" should therefore be restricted to the outcome of precise experiments: a heterologous allotransplant in the same embryo, similar to that performed by Spemann and Mangold. (Arias and Steventon 2018)

While this looks like a conception of the organizer that was corrected in hindsight with the benefit of recently acquired knowledge, I wish to claim that what Arias and Steventon refer to here is *one* sense of the term "organizer" that was always there in experimental embryology. Of course, although various biologists (Spemann and Waddington in particular) also used the term in a richer theoretical sense, a sense that imbues the dorsal lip tissue with some causal power or another, the only *uncontroversial* sense was an operational one. According to this sense, an organizer is just a tissue that has the causal power of changing the fate of recipient tissue to which it is grafted such that a new body axis formed there.[16] Thus, an organizer is defined operationally by this experimental test.

Furthermore, it had always been clear to Spemann that the host tissue must be competent to be induced; the formative power does not reside in the inducing tissue alone. However, his idea that the organizer caused neuralization of tissue that was initially committed to become epidermis turned out to be false. Spemann and other classical embryologists had always thought that the dorsal cells where the neural tube will form are initially committed to become epidermis and are induced to the neural pathway by the organizer. However, it was shown later that it was the other way around: the dorsal cells are committed for the nervous system from the beginning; what the organizer does is to antagonize signals that would change their fate to become epidermis (Gilbert and Barresi 2016, 355).

The upshot of this discussion is that there is no causal role that was uncontroversially attributed to the organizer. By a "causal role," I mean something like a specification of the concrete developmental events that the organizer causes, something like neural induction. As I have shown in the previous section, all that was really known was the end result of the organizer's activity in transplantation experiments (i.e., a secondary embryonic axis formed). Insofar as it was accepted by the CEE community, the concept of organizer was operational; organizers in various species were detectable by certain transplantation experiments, and this is what defined them. However, as I will show in the next section, these operational concepts were important for scientific practice because they gave the scientists important hints where to look for the causes of morphogenetic processes. The case is similar to the case of the classical gene, which was also a purely operational concept and which eventually led biologists to the molecular genes. Thus, while an account of reduction such as Kim's works for neither case, the heuristic function of these operational concepts is undeniable.

In the following section, I will show that there is nonetheless an important kind of inter-level relation between CEE and molecular biology, a relation that is also present in classical and molecular genetics. But this is not a relation at the level of theoretical knowledge; it inheres rather in the practice of CEE, classical genetics, and molecular biology.

4. THE ORGANIZER AND INTER-LEVEL INVESTIGATIVE PRACTICES

There is no doubt that since the heyday of CEE, molecular developmental biologists have made considerable progress in identifying some of the molecules that are responsible for the phenomena discovered by the older experimental approach. Eye induction was shown to be mediated by gene products from the *Otx2, Pax6,* and *Lens1* genes, which seem to give epidermis cells the competence to induce lenses. When this tissue comes into contact with the optic vesicle, the genes *mafs, Soxs,* and *Prox1* are activated, which in turn activate the expression of crystallin genes needed to build the lens and the retina (Ogino and Yasuda 2000). Remarkably, strongly homologous genes are involved in eye development in the entire animal kingdom (Halder, Callaerts, and Gehring 1995).

In the case of the Spemann organizer, there is a whole plethora of secreted signaling molecules and transcription factors that were described since the

mid-1980s. One of the more surprising findings was that many of the proteins produced by the organizer are growth-factor antagonists that compete with growth factors such as bone morphogenetic proteins (BMPs) for binding to their specific receptors. In the dorsal ectoderm (i.e., the region near the organizer), the effect of these BMPs is to block the neural developmental pathway to which these cells are committed. When the organizer becomes active, it secretes growth factor antagonists such as Noggin, Chordin, and Follistatin. These antagonists compete with the BMPs for their receptors and thus lift the block, thereby inducing the cells to become neural. It should be noted that before the age of the molecules, embryologists had thought that the dorsal cells are committed to become epidermis and what the organizer does is to change their fate to the neural pathway. According to molecular developmental biologists, this story is not correct: what the organizer does is to antagonize signals that commit the cells to become epidermis, thus allowing the neural default pathway to become active. Thus, the developmental role of the organizer tissue was falsely described. It is therefore not a case of functional reduction sensu Kim, according to which scientists discover the molecular realizers of previously known functional roles.

Just as an aside, it is my contention that the main reason why the molecular accounts are superior to the explanations provided by CEE is not that the molecular level is more "fundamental"—an obscure notion. Rather, it is the increased manipulability of the embryos and the developmental processes that comes with the molecular techniques. Molecular biology succeeds because it allows more different kinds of interventions (e.g., on genes, mRNA, proteins) as well as interventions that are closer to the ideal of a "surgical" intervention in the sense of Woodward (2003). An example would be the injection of a single mRNA species into an embryo (see later) as opposed to the grafting of a whole tissue. In addition, the causal links discovered were more direct. Some of them may also be more specific, which roughly means that the cause variables allow more fine-grained control over their effect variables (Weber 2006; 2017; forthcoming; Waters 2007; Woodward 2010; Griffiths et al. 2015). But these claims are not my focus in this chapter, and I shall not defend them here.[17] What I would like to consider instead is the role that the legacy of CEE played in making the molecular tools available for experimentation in the first place.

Before the 1980s, attempts to isolate some of the substances that might be responsible for processes like eye induction or the establishment of embryonic axes by the organizer failed, probably due to the extremely low

concentrations in which these are present in embryonic cells. This situation changed dramatically with the advent of molecular techniques such as gene cloning and sequencing, transgenic organisms, or antisense RNAs (small RNAs that can specifically neutralize messenger-RNAs in the cell by forming double strands with them, thus rendering them inactive). With respect to developmental biology, two advances deserve special attention here:

(1) The cloning of the first developmental genes in the fruit fly *Drosophila* by brute-force approaches such as "walking on the chromosome," using the vast collections of available *Drosophila* mutants that show developmental abnormalities (Weber 2004). The first *Drosophila* genes cloned turned out to be extremely helpful for cloning developmental genes in other organisms as well (*Xenopus*, humans, mouse, zebrafish) because it turned out that they share highly conserved functional DNA elements such as the homeobox (Gehring 1998).
(2) The invention of cDNA cloning (the "c" stands for "complementary"), a technique that uses the enzyme reverse transcriptase isolated from retroviruses in order to make DNA copies of mRNAs (Maniatis et al. 1976). The DNA copies can then be inserted in bacterial plasmids for amplification, sequencing, and making transgenic organisms.

These two methods were instrumental for isolating some of the very first vertebrate genes implicated in the organizer phenomenon. For example, in 1992, the laboratory of Edward M. De Robertis cloned a gene called "*goosecoid*" (Cho et al. 1991). (The name is a fusion of the two *Drosophila* genes *gooseberry* and *bicoid,* which both show sequence homologies.) The technique they used is quite remarkable: They isolated messenger-RNA (mRNA) from the dorsal lip of the blastopore of *Xenopus*[18] gastrulae. From these mRNAs, they synthesized cDNA. Searching these cDNAs for sequence homologies to *Drosophila* homeobox-containing genes led them to a gene that is expressed specifically in the organizer region. Microinjection of *goosecoid* mRNA to the ventral region of *Xenopus* embryos mimicked the action of the Spemann-Mangold organizer (Blumberg et al. 1991; Cho et al. 1991; Robertis et al. 1992).

Another example is the cloning of the gene *noggin.* The laboratory of Richard M. Harland used a technique called expression cloning, making use of a repertoire of effects that were already known to classical embryologists: When treated with lithium chloride (LiCl) before gastrulation, amphibian

embryos become "dorsalized," that is, all their cells form neural tissue. When the embryos are irradiated with UV, they become "ventralized," which is the opposite effect. Smith and Harland (1992) extracted mRNA from LiCl-treated cells and used it to construct a cDNA expression library. This means that the cDNA fragments were inserted into a bacterial plasmid that contained the necessary signals for any gene contained in it to be expressed. These plasmids were then injected into ventralized embryos to check for their ability to rescue the formation of dorsal mesoderm. Thus, a gene called *noggin* was isolated and shown to be expressed specifically in the organizer region in normal embryos, all over dorsalized embryos and not at all in ventralized embryos. This strongly suggested that *noggin* somehow helps controlling the pathway leading to neural development.

I will not be concerned with the wealth of molecular detail that was discovered subsequently, nor do I want to understand here what exactly these molecules and their interactions explain and how they explain it. As Waters has shown for the case of classical genetics (see section 1), we will miss all the action when we focus on explanatory relations alone. In my 2004 work, I have shown that the first genes involved in *Drosophila* development were isolated with the help of what I then called "hybrid techniques," techniques that combine methods from classical genetics and cytology with the new recombinant DNA technology. Here, I would like to introduce the idea of an inter-level investigative practice. By this, I mean practices that integrate experimental manipulations targeting different levels, such as the tissue or cellular and the molecular level.[19] Such practices played an important role in the early days of molecular developmental biology, for example, when the first *Drosophila* genes were cloned. For example, genes like *Antennapedia* or *Fushi tarazu* were first mapped genetically, using classical recombination mapping. Then DNA isolated from chromosome preparations was cloned and hybridized to giant chromosomes, using radioactively labeled DNA in order to visualize the chromosomal location on microscopic images of the giant chromosomes. This is an inter-level practice because higher-level structures, namely cytological chromosome preparations, were manipulated in the same experiment as micro-level entities, namely DNA.

The techniques used to clone some of the first *Xenopus* genes involved in the organizer phenomenon also constitute an inter-level practice. As we have seen, the blastopore lip tissue that revealed some of its causal powers in the classic Spemann-Mangold experiment was used to extract mRNA for cDNA cloning. This required the same kinds of manipulations as those applied by

the classical embryologists. But it also required manipulations on the DNA molecules, for example, by treating the extracted mRNA with reverse transcriptase in order to synthesize cDNA. This combining of manipulations at different levels is what defines inter-level investigative practices.[20]

What is most important is that the success of this practice does not depend on there being reductive relations such as they were imagined by philosophers such as Kim's functional reduction using the concept of realization, Nagel's derivational reduction, or Putnam's (1975) and Kripke's (1980) a posteriori identity such as "water = H_2O." It also doesn't require that there be some kind of general structure of reality (Waters 2017). All that it takes is some significant overlap (no coextension or set inclusion) between the things picked out by the operational concepts (organizer, induction, gene) and the molecular components that are responsible for the phenomena in question. This appears to have been the case in genetics: some but not all of the map regions where classical techniques indicated the presence of a single gene were shown to contain a molecular gene (and, of course, many molecular genes could never have been found by classical techniques because they don't produce usable mutations). It is also true in the case of the organizer: the region identified by Spemann and Mangold roughly (but not exactly) corresponds to developmentally relevant regions of tissue-specific gene expression that have an effect on the fate of surrounding cells. The operational concepts used by the classical experimental sciences were sharp enough for playing an important heuristic role in research, but this doesn't support a more traditional kind of reduction or the metaphysical assumption of a general structure (Waters 2017).

5. A TALE OF THREE SCIENCES

As we have seen, there are considerable parallels between the case of classical genetics and classical experimental embryology, both in their relationship with molecular biology.

First, in both cases, there was a body of knowledge generated by experimentally manipulating living organisms. Both sciences discovered organismic parts that have certain causal powers, namely the power to cause phenotypic differences in defined environmental and genetic contexts (in the case of genes) and the power to change the fate of surrounding cells (in the case of the Spemann-Mangold organizer or the optic vesicle). However, not many causal variables were known at the time, and the causal relations between them were quite remote. In other words, what experimenters

in the classical disciplines saw were merely the remote effects of highly complex webs of causal influence. Molecular biology identified some of the more proximate elements in these causal webs, such as transcription factors that bind to DNA and regulate gene activity. Thus, there were some weak explanatory relations between the older science and molecular biology.

Second, in both cases, there were entities for which there was a precise operational definition (i.e., protocols and criteria for experimentally identifying them) but no clear functional definition (i.e., a description of the entity's proximate causal role in the organism). Instead, there was a lot of theoretical speculation that wasn't part of a scientific consensus. If there was a scientific consensus, it covered at most ways of practicing the science and judgments about significant research problems.[21] Third, as a consequence of the previous point, there were no molecular realizers of previously known functional roles identified. Thus, there is no Kim-style functional reduction.

Fourth, there existed (and still exist) inter-level investigative practices that combine experimental manipulations on whole organisms or organism parts (e.g., embryonic tissues) with interventions at the molecular level. In the case of developmental biology, these inter-level practices were instrumental for identifying hundreds of proteins and protein-coding genes. Fifth, the molecular techniques widened the scientists' repertoire for targeted interventions that allow them to discover much more detailed networks of causal dependencies than was possible in the classical era of experimental embryology. The interventions enabled by molecular techniques were more surgical, there were more of them, and the causal dependencies discovered were less remote and more stable.

So there are considerable similarities between classical genetics and classical experimental embryology. However, there is also an obvious difference: genetics was and is a much more versatile tool for biological research than any of the techniques that were used in the classical era of embryology. Classical genetic methods, in particular the analysis of spontaneous mutants in a variety of different species, have been used with success not only in developmental biology but also in biochemistry, cell biology (e.g., Nurse 1975), behavioral biology (e.g., Konopka and Benzer 1971), and even evolutionary biology (e.g., Dobzhansky 1937). There is hardly any part of biology that has not been changed considerably by the techniques of classical genetics and the inter-level investigative practices to which it gave rise.

Another potential difference concerns the lower-level science (i.e., what would have been called the "reducing theory" in older discussions of reduction in science). As Ken Waters has shown, molecular biology provided a

basic theory about how DNA as the genetic material is replicated and expressed. However, unlike so-called "fundamental" theories (as they are thought by some to exist in physics), this basic theory is not able nor does it aspire to explain all the phenomena in its domain. It only explains how DNA molecules can be copied to produce new DNA as well as RNA molecules with the same or a complementary sequence (including repair mechanisms), how RNA molecules are processed after transcription, how proteins are synthesized, and how these processes are regulated. This is a crucially important insight for understanding life processes, but it doesn't account for everything there is in biology (in the sense in which a unified field, if it existed, would account for all physical phenomena; see Weinberg [1992]). In any case, according to Waters, molecular biology's importance is not exhausted by the explanatory achievements of its basic theory. What is at least as important is the way in which it has expanded the biologist's repertoire for learning more about processes that lie outside the scope of the basic theory.

It is not a trivial task to find out if there is anything in molecular developmental biology that would correspond to Waters's basic theory of molecular biology, as the question if and in what sense developmental biology (or any other part of biology) might have theories has been controversially discussed.[22] It is not so clear what sort of thing deserves that honorific title and what is better just described as a hypothesis or a model. For the purposes of this chapter, nothing hinges on this question. What is clear is that molecular developmental biologists heavily use not only the experimental techniques from molecular biology but also the latter's knowledge about how genes are expressed and regulated, including processes such as RNA splicing, post-translational modifications, or DNA methylation, and how proteins can transmit signals within or between cells. This is the same as Waters's basic theory. In addition, they use knowledge that is more specific to animal development, for example, about proteins that mediate mechanical adhesion between cells. Thus, they use something like an extended basic theory.

What is important for the purposes of this chapter is that developmental biologists use the basic theory and its extensions not only for *explaining* developmental processes but also for *doing* things in the lab, in particular for designing experiments to learn more about these processes. A beautiful example of this is provided by the example of the expression cloning of the gene *noggin* that I briefly explained in section 4. In this technique, mRNA was first isolated from frog embryos. Then the enzyme reverse transcriptase was used to make DNA copies of these mRNAs. Finally, an in vitro

protein-synthesis system was used to make the corresponding protein and check its biological activity in the developmental process. Theoretical knowledge and experimental techniques go hand in hand here to reveal causal effects of genes and proteins on the developmental process that were previously unknown. Thus, developmental biology was adapted to the universal toolbox of molecular biologists. Some of the older techniques such as Spemann's transplantation methods continued to be used at least for some time, much like in the case of classical genetics, but unlike the latter, they remained quite specific to the developmental biology of vertebrates.

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NOTES

1. When I was an undergraduate student in biology in the 1980s, we were even told by one of our professors that whenever we find ourselves being bored in class, the most probable cause will be that the material presented to us makes no reference to molecules!

2. See Nagel 1961 for the canonical formulation and Dizadji-Bahmani, Frigg, and Hartmann 2010 for a recent defense of this view.

3. Classic examples of bridge principles include the equation relating temperature and mean kinetic energy in an ideal gas and entropy and the probabilities of finding a system in a set of defined microstates.

4. To my knowledge, this point was first made by Vance (1996).

5. In an earlier work, I gave a similar account of how *Drosophila* geneticists used the techniques and resources that came with their model organism

in order to identify the first molecular genes implicated in development (Weber 2004).

6. The difference between Roux's frog and Driesch's sea urchin results later turned out to be an experimental artifact created by Roux's method of punctuation. If the dead blastomere is properly removed from the embryo, which Roux didn't do, the frog and sea urchin embryos respond rather similarly to this kind of intervention (Maienschein 1991, 50).

7. An insider's account of Spemann's and Mangold's work by another student of Spemann's can be found in Hamburger 1988.

8. From its inception, Spemann's model of lens induction has been embroiled in controversy (Saha 1991). Some results indicated that the optic vesicle was not necessary to induce a lens. (So-called "free lenses" were observed repeatedly by several experimenters.) Furthermore, the experiments purporting to demonstrate the sufficiency of neural tissue to induce a lens in ectoderm were not entirely conclusive because it could not be ruled out that it was contaminated by ectoderm that was already committed. Indeed, this turned out to be the case. In the 1980s and onward, new methods for marking and tracing host and donor tissues in transplantation experiments (e.g., by using dyes or specific antibodies) allowed to determine more precisely at what stage the head ectoderm becomes competent for induction (Saha, Spann, and Grainger 1989; Grainger 1992). This work led to a multistep model of induction according to which both the neural tissue and the ectoderm receive several induction signals. Spemann's own view as articulated in his *Experimentelle Beiträge* monograph of 1936 was quite close to this model; however, Spemann may not yet have had the evidence for his view. Molecular studies done since the 1990s revealed a complex cascade of mutual interactions between the neural and ectodermal cell lineages that are now referred to as "mutual inductions" (Gilbert and Barresi 2016, 523; Ogino et al. 2012). This is considerably different from the initial idea of an asymmetric induction, but Spemann & Co. were right that there was causal interaction between the neural and ectodermal cell lineages.

9. This concept of causal specificity is due to Waters 2007 and Woodward 2010. In my 2022 work, I argue that Spemann defended the organizer concept by presenting it as a (somewhat) specific cause.

10. I hesitate to characterize this remoteness in terms of stability as Woodward (2010) does because I am not convinced that longer causal chains are necessarily less stable.

11. Indeed, De Robertis's remark about the Spemann-Mangold organizer "setting developmental biology back for 50 years" suggests that the famous experiment did not show much more than was already known to Driesch, namely that a group of cells' fate can be modified by the surrounding cells. It just showed this in a very dramatic way.

12. Hoyningen-Huene (1997) argues that pheromones provide a good example of a functional role for which a set of molecular realizers was identified. He emphasizes in particular that the realizers need not themselves constitute natural kinds, as many accounts of reduction require.

13. While Kim's account is designed to be able to deal with multiple realizations, this isn't an instance. To see this, compare it to the case of pain, which is thought to be multiply realizable. Thus, pain may be defined as having the property P_1 or P_2 or . . . or P_n in the reduction base domain such that the P_i exerts causal role C. The causal role of pain may be roughly described as the property of being caused by tissue damage and causing withdrawal behavior and screaming. However, note that, by definition, *all and only* the physical states that exert role C are pain. By contrast, not all states that can be said to encode or transmit genetic information are genes (e.g., DNA methylation states).

14. Sophisticated versions of operationalism about scientific concepts to which I am sympathetic have been worked out by Feest (2005; 2010) and by Chang (2007).

15. I am indebted to Bengt Autzen and Janella Baxter for pushing me to clarify this point.

16. In my 2022 work, I argue that organizer tissue supported causally specific interventions—in other words, interventions that allowed experimenters to control the outcome in a fine-grained way. This suggested *some* role in structuring the developmental process, but it wasn't clear what role exactly.

17. Waters 2008 hints at a similar idea.

18. *Xenopus laevis* is the African clawed frog, which became an important model organism for vertebrate development. One of its main advantages is that it breeds all year round, being a tropical species. Spemann and colleagues could only do experiments with their northern newts in spring.

19. The extent to which the world is neatly divided into levels has been called into question. (For a challenging discussion, see Potochnik 2017.) I use the term "level" here mainly to refer to the domain of objects that the different sciences study (by their own lights). CEE studies embryonic tissues and

cells; molecular biology studies molecules. Inter-level practices intervene on both kinds of objects. Those who are skeptical of levels could think of them simply as domain-crossing practices.

20. Inter-level investigative practices in my sense do not necessarily involve inter-level experiments in the sense of Craver 2007. In such an experiment, an entity at some level is used to manipulate an entity at a different level. My inter-level practices do not require such inter-level interventions, although I don't want to rule them out. All they require is that interventions at different levels are part of the same practice, where practices are individuated by their goals (e.g., cloning genes involved in development).

21. I tend to think that there was less consensus than in Kuhn's influential image of "normal science," but this would have to be investigated more closely.

22. See Minelli and Pradeu 2014, in particular the contributions by Thomas Pradeu and Alan Love for differing views about this topic.

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