UNDERSTANDING

DEVELOPMENT

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Foreword

Alessandro Minelli has written an exceptionally rich book with great insights. *Understanding Development* shows that in contrast to our adult-centric and anthropocentric view of development, there is a variety of developmental processes in nature. The author effectively debunks numerous misunderstandings about development, some of which you may never have thought of before. The whole book is structured in such a way that all misunderstandings are explicitly discussed and addressed one after the other. In doing so, the author provides exceptionally clear examples from a variety of organisms, which clearly show the complexities of developmental processes and his exceptional knowledge of the topic. Minelli takes readers on a delightful and informative voyage across all forms of life and shows that development can be quite different from what we know from our own experience. He effectively makes the case that to understand life we need to look at other forms of life and their developmental processes. The present book is a fantastic means for doing this; once you have read it, you will feel stunned by the unity and diversity of life that are presented throughout.

Kostas Kampourakis, Series Editor

not be dictated by taxonomic subdivision, but by the problems to be faced to lighten our vision of development from a long list of preconceptions and unjustified generalizations, unfortunately shared by a number of professionals.

Life is a product of history. This cannot be ignored in the fields of developmental and evolutionary biology, the scope of which is the study of change. Therefore, developmental biology cannot omit a systematic exploration of the many different forms in which development takes place in the different groups of living beings.

In Chapter 1, in addition to providing a historical framework, I discuss a possible definition of development and the need to abandon the finalism still latent in developmental biology today. In later chapters I discuss cells (Chapter 2), embryos (Chapter 4), developmental sequences (Chapter 5) and genes (Chapter 6). I do this not to summarize the notions that modern textbooks present with all the necessary technical detail, but rather to address, at each level, the most serious generalizations. The remaining chapters are dedicated to aspects that, in different ways, also affect the philosophy of biology. I discuss here individuals (Chapter 3), regularity of form (Chapter 7) and developmental ecology, with several pages dedicated to temporal aspects such as age, senescence, and the articulation of individual development into a sequence of steps (Chapter 8).

In 1802, Treviranus and Lamarck introduced, independently, the name 'biology' for the science of living beings. More than 200 years later, the time seems to have come to approach biology as the science of all life forms and to avoid reducing it to abstract generalizations.

In the following pages there are rather more stories about animals than about plants, fungi and other kinds of organisms. In part, this is justified by the amazing wealth and complexity of developmental patterns and processes exhibited by animals; in part it is the consequence of my professional rooting in zoological disciplines. This bias notwithstanding, I hope that the reader will share my fascination with the inspiring disparity of developmental mechanisms behind the 'endless forms most beautiful' that evolved along all branches of the tree of life.

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1 Defining Development, if Possible

Development of What?

Development Is Not Necessarily the History of the Individual

At the beginning of our exploration of developmental phenomena, it seems reasonable to address a semantic question: what do we mean by development? Let us focus on the development of living organisms, without worrying about what development may mean, for example, to an economist or an educator.

What can be considered as development is a controversial issue. A few years ago, a group of biologists and philosophers of biology thought it necessary to consider this question seriously. Overall, the debate involved 24 scholars. Two important things emerged from their responses. First, only half of those concerned said that a definition of development was necessary; the others argued that they could safely do without, and one even added that a definition of development is impossible. Second, the proposed definitions were very different from one another, to the point that several important biological phenomena would fall within the sphere of developmental biology for some scholars but not for others.

A look at the list of proposed definitions is useful. It will serve as a guide for our itinerary, not so much to seek answers to our questions as to widen horizons as much as possible and to try to formulate sensible questions. Here are the definitions as proposed. Development is. . .

- the process by which a single cell gives rise to a complex multicellular organism;

of this book, there will be space both for individual stories (often very different from what we might describe as the normal development of an individual of our own species) and for developmental processes as such, over a time span that may be shorter or longer than one generation.

Debunking Adultocentrism

Development Is Not Necessarily the Sequence of Changes from Egg to Adult

When we describe an animal or a plant as a 'monster', this is because it departs significantly – although sometimes in one feature only – from the morphology of a typical individual of the species. A calf should have one head rather than two; a fruit fly should have two wings rather than four, as found in a well-known mutant. However, it is not always easy to say what the typical structure of an animal should be.

First, an animal may undergo metamorphosis over the course of its life. A newt, for example, spends many weeks as a tadpole, and the differences between tadpole and post-metamorphic newt are important: the tadpole is an aquatic animal that breathes through gills, while the adult can move on land and breathes through lungs (and skin).

A tadpole and a newt are the same animal; nevertheless, when we identify in the adult morphology the form typical for the species, we give the adult form an absolute value. The egg and the embryonic stages, to continue with larva and juveniles, are thus downgraded to mere preparatory stages. The 'true form' of the newt is the form of the adult. This is acceptable in the everyday use of the term 'newt', but not if we want to understand developmental biology.

As in other situations (I will give more examples in this book), useful suggestions come from the study of individuals that have undergone a less than normal development. Some newts, for example, become sexually mature without having undergone metamorphosis: they retain their larval shape and continue to increase in size, while their gonads mature as in a normal adult. If we follow the standard terminology, these newts, although able to reproduce, are not 'real' adults. The 'true form' of the animal is another.

Second, there are organisms in which it is impossible to recognize a standard form. The tiny fungus *Candida albicans*, for example, can easily switch between a single-cell form, comparable to a yeast, and a filamentous, multicellular one (see p. 27).

When discussing development, it is critically important, even if difficult, to move away from the traditional attitude that deserves the name of adultocentrism, according to which all the embryonic, larval and juvenile stages – and the developmental processes in which they are involved – are only steps or means required to become an adult. This old attitude has not changed much with the modern concept of development as the deployment of a genetic programme, because the latter is intended as a programme for the production of an adult.

In the traditional adultocentric view of development:

- The adult condition is the goal to be reached. However, we will see that this is not always true; moreover, the very notion of adult is sometimes problematic.
- Once the adult condition is reached, development is stopped. If life extends beyond the reproductive stage, the adult faces ageing – a phenomenon that traditionally belongs to the discipline of pathology rather than to the biology of development. But we will see that changes in the organism in post-reproductive age occur according to processes of the same nature as those that characterize previous stages.
- Developmental mechanisms have been consolidated through natural selection, therefore they are adaptive. But we will see that from the point of view of the cellular or molecular mechanisms involved, 'normal' developmental processes and phenomena such as the production of tumours are not necessarily very different.
- The sequence of events that characterize an individual's development is irreversible. On this topic too we will have something to say.

It is difficult to deny that the adultocentric vision contains a good deal of finalism. From this point of view, a comparison between developmental biology and evolutionary biology can be interesting. In the latter, finalism survives only in rather superficial popular versions of the theory, in which evolution is considered synonymous with progress, rather than a continuous and always imperfect adjustment to the changing conditions faced by a population. In developmental biology, however, sentences with a finalistic flavour often come from the pen of authoritative scientists. For example, Eric

Davidson, a scholar to whom we owe major achievements in the molecular genetics of development, wrote that "development is the execution of the genetic programme for the construction of a given species of organism," and that "a particular function of embryonic cells is to interact in specific ways, in order to generate morphological structure."

Also adultocentric is the term 'set-aside cells'. This designates groups of cells found in the larvae of many invertebrates, which are not parts of the larva's organs but remain dormant until metamorphosis. Only at this point, while the larval structures are reabsorbed or lost, does the adult take shape precisely from those cells that, until then, had been 'set-aside', almost with the intention – one might say – of using them later in adult morphogenesis. It would be preferable to say that those cells, rather than set-aside, were temporarily marginalized from active life.

An adultocentric view of development requires that each phase be compatible with the next. In my view, the opposite perspective is much more reasonable: that is, development can proceed so far as each phase is compatible with the previous one. In this perspective, there is no difficulty in including in developmental biology the individual stories that stop before the adult condition is reached. I am referring not just to the philosophically uninteresting case of a developmental history truncated by accident, but to stories in which, through intrinsic causes, development is arrested in a condition other than the normal: the so-called 'monsters'.

Disregarding those created in the lab (often invaluable for the progress of developmental biology), monsters sometimes show up in nature, even in our species. Their study is the subject of a specific scientific discipline, teratology. To approach this field, I suggest we turn the pages of the first treatise on comparative teratology (three volumes of text plus one of plates), published in the years 1832–37 by Isidore Geoffroy Saint-Hilaire. In this work, monsters are arranged according to a classification similar to Linnaeus' distribution of animal and plant species. This exercise is very important: if monsters can be classified, this means that their deviations from the normal condition are not arbitrary, but fall within a finite, perhaps small, number of kinds. And even monsters usually obey the laws of biological form, including two-headed calves or fruit flies with the antennae replaced by two legs, at least in so far as they do not depart from bilateral symmetry.

Growth Trajectories

There Is Not Always a Species-Specific Limit to Individual Growth

In 1864, a year before succeeding his father William as the director of Kew Gardens – one of the most prestigious botanical institutions in the world – Joseph Dalton Hooker, one of Charles Darwin's closest friends, described under the name of *Welwitschia mirabilis* a truly unusual plant discovered 5 years previously by the Austrian botanist Friedrich Welwitsch. The homeland of this unique plant is the desert that extends along the border between what are today Namibia and Angola. Its massive woody trunk, which has no branches, resembles a low stump a few tens of centimetres high. From its upper margin sprout two broad ribbon-shaped leaves, each of which can be up to 4 metres long. The tip, which is the oldest part of the leaf, is dry and frayed, especially in older plants. But the two leaves continue to grow, thanks to the proliferative activity of basal cells, throughout the life of the plant. Specimens a thousand years old are not uncommon, and some are believed to be twice as old.

Welwitschia mirabilis is the only living species of a lineage of gymnosperms – a plant with some affinity with conifers, but not very close to them. In the other major group of seed plants, the angiosperms (flowering plants), there are also a few species with continuously growing leaves: in this case, however, growth takes place from the distal tip, and the whole leaf will wither within a few years. These plants are tropical trees of the mahogany family (Meliaceae), more precisely those classified in the genera *Guarea* and *Chisocheton*.

Indeterminate growth, however, seems to be a widespread feature in trees even if, sooner or later, the process will necessarily come to an end. We will discuss in Chapter 8 whether ageing affects all living beings, or whether some organisms do not experience it. But we do not need to invoke ageing here: even the most robust tree ends up succumbing to attacks by fungi or insects, helped perhaps by severe atmospheric events.

We might think that things are different in animals. In humans, growth in height eventually slows down, then ceases altogether. Other familiar vertebrates follow the same trend. But it would not be safe to generalize. Even among mammals there are species in which growth continues throughout life, even if this slows with the onset of maturity. Examples are bison, giraffes and elephants. There are many more examples of animals with indeterminate growth among the amphibians and, more conspicuously, among fishes such as the grouper. There is also no shortage of examples among invertebrates, for example the giant clams of the genus *Tridacna*, which can live over a century, reaching enormous size. The largest known shell of a giant clam weighs 330 kilograms; the mollusc that produced it weighed perhaps another 20 kilograms.

In other cases, the arrival of reproductive maturity puts a neat end to growth, even if this was previously very rapid. Among the plants, bamboos reach the most extraordinary growth rates, up to 90 centimetres in a single day, but the plants die after their only flowering season. Animal embryos often elongate particularly fast, especially those supplied with a large amount of yolk. The increase in size of a tumour is also often very fast. In the context of normal post-embryonic development, extraordinarily rapid growth is exhibited by many tapeworms. Within 2 weeks after infection, *Hymenolepis diminuta*, a tapeworm 20 to 60 centimetres in length that lives in the rat intestine, increases 3400 times in length and 1.8 million times in weight, producing the fantastic figure of 2200 proglottids (the technical term for the 'segments' of tapeworms).

But there are also animals that go through periods of negative growth. This is not simply a matter of weight loss due to lack of nourishment for a prolonged period, but of a somewhat 'regulated', although regressive, developmental process that allows the animal to resume positive growth when environmental conditions or availability of food are back to normal. Cases of negative growth have been observed in many invertebrate groups, but we will take a look at just three examples.

Under fasting conditions, 1-centimetre-long planarians (a group of free-living flatworm, the most popular of which live in freshwater) can be reduced to a tiny worm less than a millimetre long, but their complex anatomical structure remains substantially preserved, through a proportional reduction of the various organs.

Even more intense is the effect of negative growth in some nemertines, a group of worm-like animals, almost all marine, also known as the ribbon worms. Some nemertines, for example some species of the genus *Lineus*, can endure fasting for more than a year, reducing their size from a few tens of the fibres that make up the heart mass. But this is only the tip of the iceberg. In both pythons and rattlesnakes, in conditions of prolonged fasting, the intestine undergoes morphological and functional regression; after a meal, the gut epithelium resumes its organization and functionality, not only through an increase in cell volume, but also thanks to reactivated cell proliferation. Therefore, the entire cycle of structural and physiological changes that accompany a period of fasting and the subsequent feeding phase translates into alternation between a phase of reduction and dedifferentiation and the following regenerative phase.

The next story confirms that the usual divide between development and metabolism as distinct chapters of biology is subjective. The green sea slug *Elysia chlorotica*, 2 to 3 centimetres long, is common in salt marshes and coastal pools along the eastern coasts of the United States and Canada. The species owes its specific name (*chlorotica*) to its lively green colour. This is due to the filamentous alga *Vaucheria litorea* which it feeds on without digesting it completely. After piercing the cell wall of the alga with the teeth of the scraper (technically, the radula) in its mouth, a sea slug sucks up the contents. In the mollusc's digestive tract, which has extensive ramifications throughout the animal's body, the chloroplasts of the alga remain intact for months, engulfed within the cells of the intestinal wall, and continue to perform photosynthesis. The sugars thus produced contribute to meeting *Elysia*'s food needs: we are therefore in the sphere of metabolism. But this story also affects development closely. The mollusc does not only change from a heterotrophic to an optional autotrophic condition; when it begins feeding on *Vaucheria*, its larva also finds it easier to complete metamorphosis.

Embryos, from Classic Embryology to Modern Developmental Biology

Developmental Biology Is Not the Same as Embryology

In 1673, the Italian physician, physiologist and anatomist Marcello Malpighi published a small work entitled *De formatione pulli in ovo* (On the Chick's Formation in the Egg), a true milestone in the history of embryology. The theme was not new: since Aristotle's time, the chicken had been the most accessible animal in which to study embryonic development. Even though chick embryos develop inside an opaque shell, their study has many advantages, such as availability in large numbers and, more important, the possibility of creating a rigorous time series, by incubating eggs in uniform environmental conditions and measuring the time elapsed between an egg's deposition and the moment in which its shell is broken by a scientist to observe the embryo.

In times closer to Malpighi's, other scholars such as the Italian Girolamo Fabrizi d'Acquapendente and the Englishman William Harvey had also dealt with the chick embryo. However, these authors had made their observations with the naked eye: Malpighi was the first to use a microscope. Without this tool, he would not have been able to make the observations he describes and illustrates in the 25 figures of the booklet. The chick remained the main study object of some of the great researchers of the following century, such as Albrecht von Haller, Lazzaro Spallanzani and Caspar Friedrich Wolff, and of the first half of the following century, such as Christian Pander. Karl Ernst von Baer tackled a more difficult topic, the study of the embryonic development of mammals, culminating in 1827 with his discovery of the elusive egg (or ovum) of these animals. I will look later (p. 70) into von Baer's great work of comparative embryology (two volumes, published respectively in 1828 and 1837), which represents the culmination of these studies.

In the following decades, studies extended to the embryonic development of many different animals, including a number of marine invertebrates, whose transparent eggs and embryos allow much easier observation.

Towards the end of the nineteenth century, purely descriptive study started to be complemented by experimental embryology, which we will deal with later (p. 60). The effects of manipulations (at first exclusively mechanical, later by means of chemical treatments as well), carried out at different developmental times, allowed the identification of critical developmental steps and turning points. Further advances would have to await developments in molecular biology. Scientists would eventually learn to interfere with the expression of those genes for which a morphogenetic effect is known or suspected.

Box 1.1 Animals and Plants: The Life Cycle

The developmental biology flourishing in our days is very different from the descriptive and experimental embryology of the past; however, the reader may profit from a short summary of traditional notions. The brief notes that follow describe the most frequent situations, but there are many deviations from these, several of which are discussed in this book.

In sexually reproducing animals, an individual's development begins with an egg (generally, but not always, a fertilized egg, or zygote). By repeated division of the egg, an embryo arises, consisting of an increasing number of increasingly smaller cells, the blastomeres. This developmental phase is called *cleavage*. In many animals, the embryo goes through a series of characteristic stages called the *morula* (blastomeres packed to form a compact cluster), *blastula* (blastomeres arranged in a single surface layer) and *gastrula* (a sack-shaped embryo, with only one opening, the blastopore or primitive mouth, which leads into the archenteron or primitive intestine). In addition to the two germ layers that make up the gastrula (one external, the *ectoderm*, and one internal, the *endoderm*), in most animals an intermediate germ layer, the *mesoderm*, will also differentiate. Developmental biologists use this verb to describe the processes by which a cell, tissue or body part becomes recognizably different in structure and function from the surrounding cells, tissues or body parts. During the whole embryonic development the animal relies on the nutritional resources (*yolk*) stored in the egg; as a rule, it will be able to feed autonomously at the beginning of its post-embryonic life. At this time, many animals are broadly similar to the future adult; others are very different, developing first as a *larva* that will later metamorphose to *adult*.

An animal's biological cycle typically involves the production of gametes by the sexually mature individual. The union of a male gamete and a female gamete gives rise to a zygote, with which the biological cycle begins anew.

During each biological cycle, an event (*meiosis*) occurs which gives rise to cells with the basic (haploid) number of chromosomes typical of the species (for example, 23 in humans) and an event (*fertilization*) through which the diploid condition (46 chromosomes in our species) is reconstituted by fusion of two haploid cells.

In animals, the haploid phase is limited to gametes. In plants, as described in the text (p. 50), the haploid phase is more conspicuous, especially in ferns and even more in mosses, but to some extent also in flowering plants (p. 59). Here the diploid phase (the *sporophyte*, that is, the plant with leaves, flowers and so on) clearly prevails over the haploid phase. The latter is the *gametophyte* – the pollen grain (male gametophyte, three cells) or the egg+embryo sac complex (female gametophyte, usually made up of seven cells, one of which has two nuclei). The zygote results from the fusion of the egg with one of the cells of a pollen grain.

At each transition from descriptive embryology to experimental embryology to developmental genetics, the understanding of developmental processes has risen to levels unimaginable in the previous stage. This progress, however, has been achieved at a price we are only just starting to realize. For obvious practical reasons, the number and diversity of species studied has tended to shrink. This opens an entire chapter of the life sciences – the biology of model organisms – that will be the subject of the next section.

Up to this point, we have focused mostly on animals. Until the eighteenth century, there were no important contributions to the knowledge of plant developmental biology. Even the existence of sexuality in plants was not accepted before the last years of the seventeenth century. In the middle of the following century, the eminent figure of the German scholar Caspar Friedrich Wolff emerged, author of a theory of generation based on a comparative study of embryonic development in both plant and animal species.

In plant science, the use of the term *embryo* was occasional and lacked a clear circumscription until 1788, when the German botanist Joseph Gaertner successfully used it in the first volume of his large treatise *De fructibus et seminibus plantarum* (*On Plant Fruits and Seeds*). Gaertner defined the embryo as "the most noble and essential part of the seed, the only part that provides the new plant and to which all the other parts of the seed are added for at least temporary use." Until then, there had been no name for the future seedling, in the phase in which it is still enclosed within the seed casings (integuments). It is understandable that Gaertner, faced with the uncertain nomenclature of the few accounts on the seeds of plants published before then, none of which were accurate and comprehensive, turned to animal embryology, which was undoubtedly more advanced. From this literature Gaertner borrowed many terms. 'Embryo' had long been in use to indicate an early stage of development, both of viviparous animals, including our species, and of oviparous ones, such as the chick. Of the many other terms of zoological origin used by Gaertner, some (such as placenta and cotyledon) come from the embryology of viviparous animals, others (such as egg white and yolk) from the embryology of oviparous ones. More than two centuries later, some of these terms have remained in use for both plants and animals, but nobody today would venture to say, for example, that the placenta or cotyledons of plants are the same thing ('homologous structures', to use the technical term) as the animal parts known under the same term.

Unfortunately, the idea of an equivalence between what is called an embryo in either kingdom is widespread even among professionals. To realize this, it is often necessary to lift the veil of apparent modernity provided by questions formulated in molecular terms. For example, some scientific papers address the question of whether there are similarities between the trend of gene expression along the different embryonic stages of animals and plants, but fail to explain how plant and animal developmental phases can actually be compared.

Success and Problems: Studying Development in Model Species

The Success of Modern Developmental Biology Has Not All Been Based on Model Species

What are the main model organisms used in laboratories all over the world for experimental research – the species on which is based much of what we know about development biology, and biology in general?

Among the first entries in the list, we find a few familiar animals, such as mice (*Mus musculus*) and the fruit fly (*Drosophila melanogaster*). We may not pay much attention to fruit flies as they wander among glasses of new wine or overripe fruits that are beginning to rot. However, the role they have played in genetics is well known, and this insect has been increasingly popular since 1908, when the American geneticist Thomas Hunt Morgan and his collaborators began experimenting in what has remained famous as the Fly Room at Columbia University, New York. Other model animals are less popular, but in elementary biology courses it is likely that one will at least encounter photos of zebrafish (*Danio rerio*) and of the tiny nematode worm whose scientific name is *Caenorhabditis elegans*. Among plants, the most fashionable model species is the humble thale cress (*Arabidopsis thaliana*), but also important are tomato (*Solanum lycopersicum*), snapdragon (*Antirrhinum majus*) and rice (*Oryza sativa*), plus the moss *Aphanorrhegma patens* (usually known as *Physcomitrella patens*). Let's add to this list two representatives of the fungi (baker's yeast *Saccharomyces cerevisiae* and the red bread mould *Neurospora crassa*), and the cellular slime mould *Dictyostelium discoideum*, an odd kind of organism whose life cycle will be the subject of a later section (p. 36). Discoveries based on most of these species will be mentioned repeatedly in later chapters. The problem with model species is that the results of develop into sepals, those where A and B expressions overlap develop instead into petals, those with B and C into stamens, those with C only into carpels. Important differences in the genes actually involved were soon found in the snapdragon; and in fact, the pattern of gene expression found in the latter applies to a much larger set of plant species than the pattern found in the first plant model.