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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;

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- the generation of a new individual form;
- the change of biological form over time;
- the temporal change of organization along the life cycle;
- the biological reading of DNA-encoded gene networks that determine the structure of the organism;
- the irreversible increase in the complexity of a biological system over time.

In different form, all of these definitions capture important aspects of development and many of the problems on which most research focuses. However, it is sensible that from the very first pages of this book, the reader should assume a critical attitude towards a number of positions that it is all too easy to take for granted, e.g. that

- development is a series of structural changes affecting multicellular organisms; single cells per se, including unicellular organisms, do not develop;
- development is about the biological individual – indeed, it is the process that shapes the individual;
- development necessarily entails an increase in complexity;
- the body contains (multiple copies of) a programme according to which it is formed;
- development is irreversible.

These widespread beliefs are based, at best, on a generalization of conditions that apply only to some living organisms, not to all. They overemphasize aspects that cover only a part of the phenomena that deserve to be called developmental processes.

An excellent starting point to clear the path through these problems is a few sentences by the great French physiologist Claude Bernard:

> . . . all morphological change is contained in the previous state. This work is pure repetition. [. . .] there is no morphology without predecessors. In reality we do not witness the birth of a new being: we only see a periodic continuation [. . .]. Things happen this way because the being is in a way imprisoned in a series of conditions from which it cannot escape, since they are always repeated in the same way internally and externally.

This text is from the *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux* (Lectures on the Phenomena of Life Common to Animals and Plants) published in 1878, immediately after Bernard's death.

Thus, in Bernard's vision, development is not the history of the individual from zygote to adult, but a series of changes in which each step depends strongly on the conditions in which the living organism was until then. It is like a chess game, where different choices (some more advantageous for the player, some less so, but this is not important) are generally possible with each move; these choices depend on the current arrangement of the pieces on the board and this, in turn, depends on the previous moves. The comparison between the succession of changes in development and the configurations of the pieces on a chessboard, however, is only valid as long as the game is in full swing. When the game is over, the board is emptied: there is no continuity between one game and the next, whereas there is between one biological generation and the next. It is precisely here that it is advisable to take a closer look, to make clear what should be considered as development.

In fact, we are faced with two possibilities. If we listen to Bernard, development is a process (better, perhaps, a set of processes) that continues through the generations. If instead we follow the popular notion (shared by many professionals), development is the individual story of the changes that transform an egg first into an embryo, then into a juvenile and finally into an adult.

However, there is a way to overcome this dichotomy. If we do not want to leave a good number of important topics outside the scope of developmental biology, we should accept a notion of development consistent with Bernard's observation. The chapters of developmental biology, therefore, will not be (only) those that correspond to moments in the history of an individual, such as cleavage (the division of the egg into a progressively increasing number of cells, the blastomeres) or gastrulation (the embryonic developmental phase shared by almost all animals, during which germ layers are formed; more on germ layers on p. 78). Instead, the mechanisms of regeneration will fall within the scope of this discipline, even if most of what we know about them are the responses to challenges an animal would never face in nature; or the structural changes resulting from a pathological situation, primarily cancer, or those induced by the presence of a parasite.

In this broader perspective, the history of the individual does not become less interesting or less central in developmental biology, except that the succession of stages from egg to adult animal (or from seed to mature tree) is no longer *the* development, but *a particular history* of development. In the pages 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

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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.

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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

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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 centimetres to a microscopic mass of a few hundred cells: in the process, the gonads, digestive tract and other organs are resorbed. The outcome of this negative growth can be described as a return to an embryonic level of morphological complexity.

The final example is from insects. In conditions of prolonged fasting, the larva of the small beetle *Trogoderma glabrum* progressively decreases in weight and also in length, but it cannot be said that its development is suspended. On the contrary, it goes through a higher number of moults than normal. Whereas under normal feeding conditions the larva of this insect goes through five or six stages, a fasting larva continues to moult an indeterminate number of times, even for years: after each moult, its size is a little smaller.

Uncertain Boundaries

Developmental Change Is Not Necessarily Different from Metabolism

In a part of the tree of life where the divide between unicellular and multicellular conditions is particularly thin, we find a species of tiny marine organisms known as *Salpingoeca rosetta*. This is the best studied species among the choanoflagellates, a small group of microscopic eukaryotes with some characteristics that suggest affinity with the evolutionary lineage of the animals. The trait that gives them their name is the presence of a whip-like structure called a flagellum, surrounded by a showy collar. What is remarkable, of course, is not the flagellum: flagellated cells are present in many groups of organisms, such as the spermatozoa of most animals, including humans. It is the collar that is not as common. This is a sort of circular palisade formed by microvilli, those slender rod-shaped extensions found, for example, on the side of the cells of our digestive tract that faces the lumen of the intestine, greatly increasing their surface area and therefore the efficiency of the absorption of digested substances. The cells of the gut mucosa, however, possess microvilli but not flagella. Cells similar to those of choanoflagellates are characteristic of sponges, where they are called choanocytes.

In both cases (choanoflagellates and choanocytes), the continuous movement of the flagellum and the presence of the surrounding palisade of microvilli allow for efficient circulation of water. This forwards tiny nutrient particles to the cells, which then engulf them. What makes the similarity between choanoflagellates and sponge choanocytes more interesting is that some choanoflagellates, including *Salpingoeca*, often live in groups: that is, they exhibit a rudimentary form of multicellularity. In recent years, DNA comparisons have confirmed that choanoflagellates are indeed among the closest relatives of animals. This has motivated a search in choanoflagellates for clues about the transition from the uni- to multicellular condition: for example, the presence in choanoflagellates of those molecules that allow cells resulting from a mitosis (the normal cell division that produces two daughter cells, both of them with a complete copy of the parent cell's genome) to remain together. A number of these molecules have actually been found in choanoflagellates. In the latter, however, the transition between the single-cell and the multicell organization is not an obligate developmental step, as in animals, but depends on environmental conditions. What triggers this transition? In the case of *Salpingoeca rosetta*, the stimulus is the presence of certain species of bacteria, in particular *Algoriphagus machipongonensis*. But the bacteria do not only act as the trigger of this important morphogenetic event: *Algoriphagus* is also a prey species for the choanoflagellates.

We are thus faced with a situation where one external agent serves both as food and as the trigger of a structural change – that is, it is involved both in metabolism and development. However, this is not an isolated case. Perhaps this distinction was not yet clear before the chain of transformations that we call development took on an autonomous and precise form in the evolutionary lineage of animals. Problematic situations are found almost everywhere.

Let us take snakes as an example. For a large python, coping with food needs is no small problem. Like almost all snakes, pythons are predators, and their appetite can be satisfied only by rather large prey. A python has remarkable strength, and the tightness of its turns allows it to kill a variety of prey, including monkeys and pigs. However, by the time the snake opens its jaws and starts swallowing the prey, its problems have only just begun. The victim is not chewed, cut into small pieces and suitably sprayed with saliva before being pushed down through the oesophagus; instead, it ends up in the stomach still almost untouched. Digestion, which is long and difficult, requires support from all the organs of the snake. In 2 days from the time the python swallowed the prey, the length of the intestinal villi increases fivefold and the muscle mass of the heart ventricle by 40%. This latter increase is due not to cell proliferation but to growth in the amount of contractile proteins in