JAMIE A. DAVIES

life unfolding

how the human body creates itself

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To Katie

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ETHICAL STATEMENT

This book, which describes the mechanisms of human development, includes published knowledge that has been obtained by study of human embryonic and foetal material and by experimentation on living animals. Because academic publishers and funders of research require that all work be ethically approved by the relevant independent ethics committees, I have assumed that these experiments were conducted according to the standards of the day. Ethical standards do change with time, and some work done long ago would not be permitted now. Mention of experimental results in this book does not imply personal ethical endorsement of the experimental method, by either the author or publisher.

A NOTE ON REFERENCES AND FOOTNOTES

This book is aimed at a general readership and, for this reason, the mechanisms of human development have been described with as little molecular detail as is possible. Long lists of unpronounceable protein names are tedious even to professional biologists and would be out of place in a book that is meant to present deep principles. Nevertheless, to help committed students of biology and medicine to connect the events in this book with papers on molecular embryology, occasional technical footnotes indicate which details the main text is avoiding. Understanding these technical notes is not necessary for understanding the book—they are present only for a small subset of the readership with particular needs.

For similar reasons, the main text uses superscript numbers to cite technical research references, especially in support of statements that are at variance with a traditional view. In the interests of conciseness, these citations have been kept to a minimum and, instead of following the normal academic convention of citing original experimental reports, they instead often point to review articles that provide a convenient gateway to experimental literature. No explicit citations are given for material that is well covered in standard textbooks. The alternative, of having the text interrupted by thousands of citation numbers, as would happen in a research monograph, would not be appropriate here.

A list of accessible books for further reading on particular topics is given at the end of the book.

INTRODUCTION

The possession of knowledge does not kill
the sense of wonder and mystery.
There is always more mystery.

Anaïs Nin

1

CONFRONTING AN ALIEN TECHNOLOGY

The history of a man for the nine months preceding his birth would probably be far more interesting than all the three-score and ten years that follow it.
Samuel Taylor Coleridge

When the English philosopher-poet Coleridge wrote those words, he was expressing, in the elegant language of an adult, the wonder that is felt by every child who asks his parents '*How did I get here?*'. To many parents, the question brings up potentially uncomfortable issues about sex and about when, and how much, a child should be told. To the child asking, innocent of these adult psychosocial complexities, the question is both simpler and far more profound: it is simply about how a new person can come to be.

No child has ever received a full and correct answer to the question, because nobody yet knows enough to give one. When Coleridge was writing, some facts were known about the sequence of anatomical changes that took place as a new human grew in the womb, but how or why they took place remained utterly mysterious. In the two centuries that have since passed, generations of scientists have laboured to understand how a fertilized egg can become a child. Research has pushed forwards quickly in the last decade and, as more intricate and complex mechanisms have been discovered and the mystery has decreased a little, the collective sense of awe has only increased. The story that is being unearthed, and presented so far mainly in the dry text of learned journals, is an astonishing one. It is the story of something every one of us has done, and it is therefore a story that belongs to us all. This book is an attempt, by a scientist who has the good fortune to be working in this area, to bring together highlights of recent research into that most profound, and childlike, of questions—*how did I get here?*

Our current understanding of human embryonic development has not come from a single investigative approach, but is instead emerging from a synthesis of information obtained from a range of scientific disciplines. Embryology and neonatology are concerned directly with development and produce a great deal of directly relevant anatomical and functional information. Genetics and toxicology, both fields with a scope much broader than development, have been very valuable in identifying precise causes of congenital abnormality: this is important because known causes of malformation can point developmental biologists to identify the molecular pathways that are required for the affected part of the body to grow normally. Biochemistry and molecular biology are invaluable for working out the details of how these pathways work, following the logic of development even down to the spatial scale of interactions between the atoms of biological molecules. Cell biology accounts for how molecular pathways are brought together to control the behaviour of individual cells. At much larger spatial scales, disciplines such as physiology, immunology, and neurobiology uncover the ways in which multitudes of cells communicate and coordinate.

All of the subjects mentioned so far would be found in departments of biology or medicine, the traditional homes of embryological work. In recent years, however, exceptionally valuable insights into human development have also been contributed by researchers in fields that might seem at first to have nothing to do with the topic, such as mathematics, physics, computer science, and even philosophy. These efforts have not been focussed on precise details of which cell does what and when, but have instead tackled the profound, abstract questions that development raises, including, *how can the simple become complex?*, *how can error-prone mechanisms construct something precise?*, and *is human development too complex for developed humans to understand completely?* The jury is out on the last of these questions—the word 'completely' being the point of dispute—but significant progress has been made on the other two questions, both of which find an answer in the related concepts of 'emergence' and of 'adaptive self-organization'. The terms are essentially two sides of the same thing, one viewed from above and one below. 'Emergence' tends to be used by people looking down from the perspective of high-level behaviours, and is the process by which complex structures and behaviours arise from simple components and rules. 'Adaptive self-organization' is a description grounded in the components and looks upwards, describing how the application of simple rules to these components can result in their collectively doing something large scale, clever, and subtle.* The way in which adaptive self-organization allows non-living molecules to produce a living cell, and allows cells with very limited individual abilities to produce a very able multicellular body, will form a theme that runs through all of this book because it is the core of development. Adaptive self-organization and emergence go far beyond biology, and some very readable books on its wider implications are listed under 'Further Reading'.

One very clear message that can be taken from our emerging understanding of development is that the self-construction of a body is very different from our normal notions of construction, experienced in architecture or engineering. This highlights a fact that is as important as it is ironic: the methods by which we build our own bodies seem utterly alien to us. It may therefore be useful, in preparing to understand how an embryo can build itself, to compare and contrast the biological system with human-scale construction technologies.

Engineering projects, for example the construction of a locomotive or a building, tend to share a common set of features. To begin with, there is a specific plan, set out in a blueprint or some other form of schematic, that shows a clear representation of the intended outcome. The plan depicts the finished structure but will never itself be a physical part of it. Each project has someone in overall charge, a chief engineer or an architect, and he or she operates through a hierarchy of command to pass instructions to the artisans who carry out the work of cutting, brick-laying, welding, and painting. The components that are handled by these artisans cannot pull themselves together on their own. Instead, they have to be cemented or bolted or welded by workers who remain distinct from the structure. These workers, and their chief engineer, provide vast amounts of 'outside' information, such as knowledge of the techniques for soldering or for shaping an arch, information that is not present in what they are building. Finally, most structures have to function only when they are complete.

* Synonyms for, or sub-types of, adaptive self-organization include 'swarm intelligence' and 'hive mind'. These are often used in studies of social insects or even populations of humans but use words that seem too suggestive of sentience to be applied to mere chemicals and cells. For this reason, in previous books and in this one, I have used the term 'adaptive self-organization', used more commonly in the physics and mathematical communities to refer to the same phenomenon.

Searching for any of these features in biological construction highlights just how different life is from conventional mechanical and civil engineering. Unlike engineering projects, biological construction does not involve a blueprint-like representation of the final structure. There is certainly information in a fertilized egg (in genes, in molecular structures, and in spatial variations in the concentrations of particular chemicals), but this has no simple relationship with how the final built body will look. We know that the information has the effect of controlling the sequence of events that will follow (we know because changing the information, for example by mutating a gene or by altering the location of a relevant chemical, alters that sequence and makes development abnormal).

In engineering, and especially in mathematics, a final form can be specified by a series of instructions. Telling someone to drive a peg into the ground in the middle of a wheat field, tie a rope to it, hold the other end, walk away until the rope is fully tight, then turn right and walk along so that the rope remains tight is, for example, a way of specifying the construction of a simple crop circle. Some structures can be specified much more economically by the use of instructions than by producing detailed blueprints. If you happen to have a pen and paper handy, try following these instructions to draw a geometrical figure called a Sierpinski Gasket:

1. Draw an equilateral triangle, with a horizontal base, as large as possible. Consider this the 'triangle of interest'.
2. Draw three lines inside the triangle of interest, each line going from the mid-point of one side to the mid-point of an adjacent side. These three lines will have defined a downward-pointing triangle occupying a quarter of the area of the triangle of interest.
3. Shade in the triangle you just created.
4. Observe that there are now three unshaded upward-pointing triangles within the old triangle of interest. Consider each of these a triangle of interest and go back to step 2 for each of them.
5. (Stop when you get bored: if you had a fine enough pencil, this would go on for ever.)

The Sierpinski Gasket, which would be gasket-like if the shaded areas are imagined as holes, is an example of a fractal, or self-similar, structure whose form looks similar at any magnification. Another is Cantor Dust, which can be drawn most easily on a medium that allows erasure, such as a blackboard: draw a line, erase its middle third, then erase the middle thirds of the shorter lines this erasure created, and so on. After a while, you will be left with a peculiarly spaced set of chalk marks, the intervals between which have statistical properties identical to those of a vast range of natural phenomena, such as the distribution of sizes of avalanches in a sand dune, intervals of time between drips of a leaky tap, or intervals between large earthquakes, epidemics, and major extinctions.

Even outside mathematics, the idea of specifying a constructed object by giving the rules to generate it, rather than by depicting a detailed illustration of its final form, is common. Food recipes work this way, as does textile manufacture, at levels ranging from the simple 'knit one, purl one' type of instruction set in a knitting pattern to the complicated punched cards of Jacquard's 1801 loom, the world's first programmable manufacturing robot. Music is similarly specified by instructions, in this case by dots on a stave that instruct a musician to play a certain pitch, at a certain time, for a certain duration.

Our long cultural experience with the use of instructions as an economical method of specifying an intended outcome makes it dangerously natural to accept that biological information specifies our own form by a similar process to those mentioned above. There is one critical difference: human-built objects constructed by following a sequence of instructions are read and acted on by an external, intelligent agent. Even apparent exceptions to this statement, such as a knitting machine or a player piano, rely on machines that are themselves made from plans or instructions that were read by external, intelligent agents, so they are not really exceptions. Put simply, cardigans, symphonies, cars, and cathedrals do not build themselves. Instructions, operational knowledge (the skills of knitting, cooking, welding, stone-masonry, etc.), and physical manipulation of materials all come from outside, not from within the growing structure. The information in an embryo, on the other hand, has to be read and acted upon by that embryo, with no handy external workmen to do the heavy lifting or the heavy thinking. As will become clear shortly, this means that responsibility for biological construction is shared between all of the components involved rather than, as in most technological construction, someone being in overall charge. In constructing a human being, control is not exercised by a few privileged parts but emerges from the system as a whole.

Understanding any construction process demands, in addition to other things, some appreciation of the nature of the materials to be used. Near my laboratory in the University of Edinburgh, there are three famous bridges: Thomas Telford's elegant Dean Bridge in the city itself, Benjamin Baker's iconic

Forth Railway Bridge across an inlet of the sea, and the Forth Road Bridge that now runs beside it. Telford built his bridge from stone blocks: heavy, bulky components that are safe in compression only. He therefore used the conventional method of first building the pillars, then making a wooden scaffold to set out the arch, then covering it with shaped arch stones and building up until the weight of the stone stabilized the arch and the scaffold could be removed. Baker used what was then a radical new material—steel—to construct his rail bridge. This material can be used in tension and compression, so the bridge could be built outwards from each set of piers as a cantilevered structure, cranes being used to hoist the long and comparatively light steel sections in place and rivets being used to connect them together. The suspension bridge that carries the road, the newest of the three bridges, hangs from tense steel cables that rise up to, and press down on, towers on each shore. For this bridge, the towers had to be built first, then strong anchor points were made behind them for the cables, and then the cables themselves were added strand by strand and tensioned until they were complete and the road could be hung from them. In each case, the entire strategy for building the bridge was determined by the nature of the materials, and none of the bridges could have been constructed using the strategy meant for either of the others. In biology too, the strategy for construction depends on the nature of the components involved. This is therefore a good place to introduce three key biological components that will be mentioned many times in this book: proteins, mRNA, and DNA.

By far the most important molecules in biological construction are the proteins. They make most of the physical structures that give cells their shape, they form the channels and pumps that regulate what enters and leaves the cell, and they are the catalysts that drive and control the chemical reactions of life. These reactions include the metabolic pathways that make the body's other components such as DNA, fats, and carbohydrates. The relative importance of proteins is illustrated by the fact that red blood cells naturally throw away their nuclei, containing all of their genes, during maturation, yet they continue to live for around a hundred and twenty days after doing so. A cell that kept its genes but lost the function of its proteins would be dead within seconds.

A protein consists of a long chain of individual units, amino acids. There are twenty different types of amino acid, and they vary in shape and chemical properties. They interact with one another, and this means that chains of amino acids tend to fold into complex forms, either on their own or with the temporary help of other proteins. This folding process is so involved that it is still not possible to deduce, mathematically, the final form of a protein simply from knowledge of its amino acid sequence. (Computer programs for predicting protein shapes do exist, but they use a combination of calculation and probabilistic reasoning based on the relationships between the known structures of other proteins, determined the hard way by X-ray crystallography, and their underlying amino acid sequences. They therefore operate in a manner similar to computer programs that perform weather forecasting, albeit with a little more success.)

Different proteins have different sequences of amino acids. These are added, one by one, to the growing chain of a protein as it is being made in an order that is specified by another molecule, called messenger RNA or mRNA (see Figure 1). Molecules of mRNA also consist of single chains of individual units, the RNA

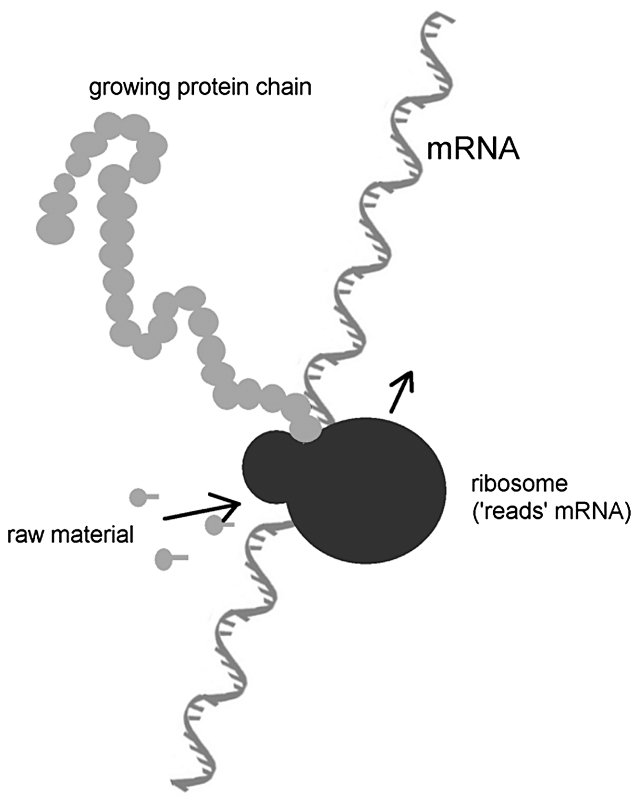

FIGURE 1 mRNA is translated into a protein by a ribosome, which assembles amino acids into a growing protein chain according to the sequence of bases in the mRNA.

bases A, C, G, and U. These are structurally similar to each other and, compared to amino acids, chemically rather dull: molecules of mRNA do not do much in the cell except for directing the sequence of amino acids to be added to a growing protein. This sequence is determined by the sequence of bases in the mRNA, a group of three bases specifying each amino acid.

The sequences of bases in molecules of mRNA are determined directly by the sequences of DNA bases. DNA is a very long molecule consisting of a succession of four bases, A, C, G, and T, which can be accommodated in any sequence. The individual DNA molecules that form the cores of the forty-six chromosomes in each of our cells are many millions of bases long. Within these are the stretches that constitute individual genes. When a gene is being read, an RNA molecule is made such that it copies, in the language of the RNA bases A, C, G, and U, the order of the DNA bases A, C, G, and T. The RNA is therefore effectively a copy, or 'transcript', of the gene in a different medium. The actual reading of genes is performed by complexes of proteins. These first bind to various short sequences of bases such as ATAAT, or TCACGCTTGA, which can be found near the start of a gene. Different genes have different combinations of these short sequences near them, and each sequence binds its own particular protein, so different combinations of proteins are involved in activating the reading of different genes.

The fact that different genes are activated by different DNA-binding proteins is important because different cells of the body need to make different types of protein. Cells in the gut, for example, make proteins that digest food, cells in the ovary express proteins that make reproductive hormones, and white blood cells make proteins that fight infection. All of these still contain all of the genes of the genome, even those that they never use. Only the genes that the cell needs are read, because only the set of DNA-binding proteins that recognizes exactly those genes is present.

This is where we are forced to abandon the idea of any one of these components being in overall charge of a cell, or of an embryo. To recap: proteins are made only because active genes specify (via mRNA) that they should be made. Those genes are active only because proteins already present make them so. The logic is therefore circular: control is located nowhere, because control is located everywhere (Figure 2).

The circularity of Figure 2 has an interesting implication. For a cell to remain in a stable state, the total set of active genes must include those that specify the proteins that bind to recognition sequences near those very genes, but must *not*

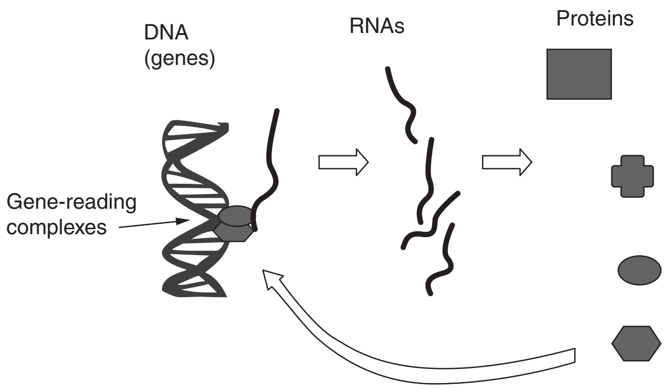

FIGURE 2 The circular nature of biological logic. Proteins decide which genes are read, and these genes specify the production of new proteins, some of which decide which genes are read . . . and so on.

include any proteins that will activate currently inactive genes. Unless these conditions are met, the proteins made by the set of genes active now will not sustain that set of genes—some genes may go off and others on, and a new set of proteins will be made, and so on. These changes will continue to take place until a self-sustaining state is reached. This is the basis of how, as we develop, some of our cells change to become new cell types. Such change is driven typically by external influences, 'signals', that alter the ability of specific proteins to activate genes: these disrupt what was an existing stable state, and make it shift to a new state. Many examples of such signals will feature in the rest of this book.

Distributed, circular control is by no means the only strange feature of biological construction. Another feature that seems very alien, when viewed from the comfort zone of conventional engineering, is that biological molecules can assemble themselves into larger-scale structures spontaneously, something that bricks and bolts never do. This process, which is of fundamental importance for the existence of life, is a little like the formation of crystals. Ordinary crystals, such as those grown by children with chemistry sets, form because their constituent molecules can bind to each other, typically by attractions of small, local electric charges. Proteins also have patterns of intrinsic local electric charges, often in rather complex crevices in or projections from the main body of the protein. The arrangement of charges and the shape of the protein are properties that derive from the sequence of amino acids. Sometimes, a protein has one kind of crevice at its front end, and a projection that fits that type of crevice at its back end, rather like a 'Lego' brick. In that case, molecules of this

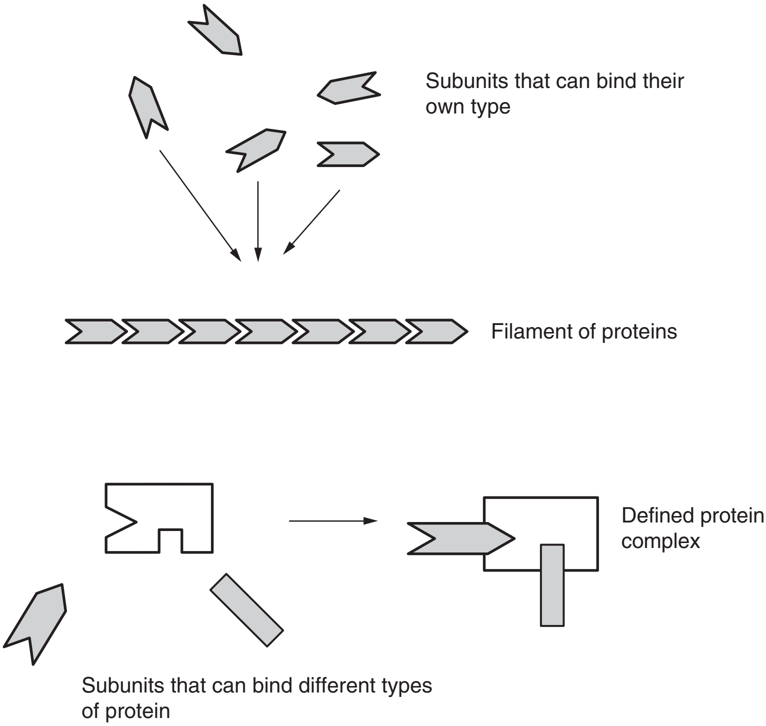

FIGURE 3 Proteins often carry charge patterns, projections, or crevices that can bind strongly to complementary charge patterns or shapes on other proteins. Where one end of a particular protein can bind the type of structure at the other end of the same protein, then molecules of this protein can form a filament, with each molecule behaving as a separate link in a chain. Where a particular protein can bind only proteins of a different sort, multi-protein complexes of a defined size and shape are created. The protein complexes that transcribe genes are of this type.

protein can line up end to end to make a long, thin filament of indefinite length (Figure 3). More often, each protein can recognize binding sites only on another specific protein, or some other molecule, and not on itself. This means that it cannot form indefinite crystal-like threads with identical molecules, but instead binds only to a defined number of other proteins to make a multi-component complex of a defined structure. These complexes are very important in the cell because they act as tiny machines that can run complex chemical reactions or organize the assembly of structures that are too large and complicated to arrange themselves spontaneously. The gene-reading protein complexes already mentioned are an example.

The level of organization represented by protein complexes takes us to a very important boundary. The assembly of proteins into their complexes relies on information that resides only within proteins themselves ('information' being, in this case, synonymous with structure). It therefore belongs within the domain of chemistry and the result is always the same: reliable, reproducible, but inflexible. At larger scales, biological structures are more variable, their exact arrangements being adapted to circumstances. The overall shape of a cell, for example, is adapted to the space it must fill in a tissue. The arrangement of the connections it makes with neighbouring cells must similarly be adapted to the location of the cells that surround it. These larger-scale structures cannot, therefore, be determined solely by the information contained in the chemical structure of their molecular components: extra information is needed. This transition, between internally determined structure and structure that is regulated by external information as well, takes us across a boundary from pure chemistry to the realm of biology. In biological systems, layers of regulation are added to chemical self-assembly to produce systems that organize structures adapted to circumstance and need. This is where the concept of adaptive self-organization, mentioned earlier, becomes important. Adaptive self-organization turns out to be the key to explaining how a few thousand genes and proteins, none of which can possibly hold any concept, in any language, of the structure and function of a human body, can nevertheless organize themselves to build one. It stands in marked contrast to the way that engineering projects use external agents, such as workmen or robots, to assemble components together in the right way. The following chapters will illustrate how adaptive self-organization is critical to human development, at levels ranging from self-organization of molecules within a single cell to the large-scale construction of complex tissues.

A final peculiar aspect of biological construction comes from a great restriction of life: it cannot be stopped and re-started to suit the needs of the building process. Human-engineered structures, such as computers and aeroplanes, are expected to function only when they have been completed: there is no need for a partially complete structure to do anything useful. Development of an embryo has the constraint that every stage of development must be compatible with its staying alive. A plumber wanting to connect a new branch to the water main of a building can shut the water off, cut through the main pipe, add a 'T' piece, then turn the water on again when the job is completed. If a growing human were to take the same approach when it needed a new branch from a main artery, it would have bled to death well before the job could be completed. The same is true for all of the other essential systems of the body. The absolute requirement for constant viability in the face of developmental change is a very serious constraint on how bodies can be built, and it is another reason that the construction of a body can seem so alien, and sometimes so complicated, when compared to ordinary engineering.

When we seek to understand our own beginnings, we must be prepared to move beyond homely analogies, based on how we build things, and see the embryo in its own terms. It will be a journey into strange territory, which demands new ways of thinking and a letting go of engineering metaphors. We do not build embryos, after all: they build us.

PART I

FIRST SKETCH

2

FROM ONE CELL TO MANY

I am large, I contain multitudes. Walt Whitman

It is one of the great ironies of biology that the human body, arguably the most complex single entity in the known universe,* develops from a very simple beginning. An adult human consists of over a million million cells—a number that is about ten times the number of stars in our galaxy or, to give a more down-to-earth comparison, about ten times the number of grains of sand on a beach volleyball court. These million million cells are not heaped up haphazardly but are located and connected in patterns so intricate that, even after two millennia of research into anatomy, we have still not worked out all of the details. There are hundreds of different cell types amongst them, each with its own function and way of living, each produced and renewed in the correct proportions and the correct places. All of this elaboration originates from one single, simple, almost-featureless cell, the fertilized egg. It is from this unassuming beginning that the complexity of a human being has to create itself—to pull itself up by its own bootstraps, as the saying goes.

The first major step towards a more complex form of being is the conversion of that single cell into a multitude. This is necessary because any complex living animal requires many different things to be going on at the same time. Right now, you are breathing air, digesting food, detoxifying chemicals, growing hair,

* Humans are singled out on the assumption that the wiring of our brains includes more underlying neural complexity than is present in other mammals, although future research may prove this assumption wrong.

making new skin cells, filtering blood, fighting would-be invaders, regulating temperature, hearing, reading, thinking and, by this stage of the sentence, probably indulging in some introspection. These activities, and hundreds of others not mentioned but happening anyway, use different sets of proteins and biochemical pathways. Many would be downright incompatible if they were to take place in the same place: consider, for example, a mother's making milk for her baby and her digesting milk she has just drunk in her tea. There are many other examples that are incompatible for more subtle reasons concerning the details of protein and gene function.

Complex organisms deal with this problem using compartmentalization, the principle of separating each activity into different places. Bodies are divided into organs that do different things, and organs are divided in their turn into tissues, which perform different functions of the organ. Tissues are divided into cells, different types of cells again performing their own specific tasks. Within each cell, though, most molecules can move around freely and it is difficult for many different things to take place at once. There are some internal compartments to cells, and the ability of different parts to perform slightly different functions will be a central theme in Chapter 8, which describes how cells move and navigate around an embryo. Even so, the ability to perform several tasks at once is limited, and the cell can therefore be considered as a basic unit that does only one or two things at a time. For this reason, having a multiplicity of different cells is an essential step in making a complex body.

The mechanisms by which one cell can become two and, by repeating this, can become many, are not only critically important to embryonic development: they also illustrate clearly how small, simple molecules can organize themselves to achieve remarkable feats at scales far larger than themselves, and how they can build structures of amazing detail with no prior plans. This idea is central to understanding the embryo as a whole. This chapter will therefore be devoted to the mechanisms of cell division, which we can then take for granted in all of the later chapters.

The fertilized egg with which human development begins is unusually large, about a tenth of a millimetre across and just visible to the naked eye. Most cells in the mature body are very much smaller, being about a hundredth of a millimetre across and having about a thousandth of the volume of the egg. This means that the fertilized egg can generate a many-celled embryo simply by dividing itself up, first into two, then four, then eight and so on, without the need to pause for growth. This form of cell multiplication, called cleavage, is very useful because it means that the business of getting food to fuel growth can be deferred until the embryo is already multi-cellular and therefore able to dedicate specific parts of itself to procuring food.

With no growth taking place, dividing one cell into two is mostly a case of sharing out all of the internal molecules, such as proteins, equally between the daughter cells. The very nature of division with no change in net volume means that the concentration of internal proteins and nutrients is unchanged. The glaring exception to this general statement is DNA: the undivided cell has forty-six chromosomes (twenty-three from the embryo's mother and twenty-three from the father), and each of the cells produced will also need forty-six chromosomes. The chromosomes therefore have to be replicated before each round of cell division begins. What is more, some system must exist to ensure that the replicated chromosomes are allocated equitably to the daughter cells, not just so that each daughter cell receives a total of forty-six, but to ensure specifically that each receives exactly one copy of each chromosome that was inherited from the father and exactly one copy that was inherited from the mother. The system that achieves this accurate separation of chromosomes is a central feature of animal and plant life and it has existed for around 2,500,000,000 years. Only for the last two million years or so has it been producing an animal capable of starting to understand it.

The copying of the DNA is in many ways the simplest part of the process, and is also the oldest, having existed in a basic form for at least 3,500,000,000 years. It uses the fact that DNA molecules exist as a pair of nucleotide chains (sometimes called 'strands'). Where there is an 'A' nucleotide on one chain, there is always a 'T' facing it on the other, and where there is a 'C' on one chain, there is always a 'G' facing it on the other. This rigid pairing rule, which arises simply from the detailed chemical shapes of the nucleotides A, T, C, and G, means that each single chain of DNA carries enough information for the sequence of its partner chain to be deduced. When a cell needs to replicate DNA, a complex of enzymes first separates the two chains. It then assembles a new partner chain for each of the originals, bringing new nucleotides together in the order determined by the order of nucleotides on each original chain. Each new chain stays with the old one that was used to specify its construction, and the result is two DNA double-chained molecules where there used to be one. The DNA has, effectively, been copied. The proteins of the chromosome, around which DNA wraps, are added once the DNA has been copied.