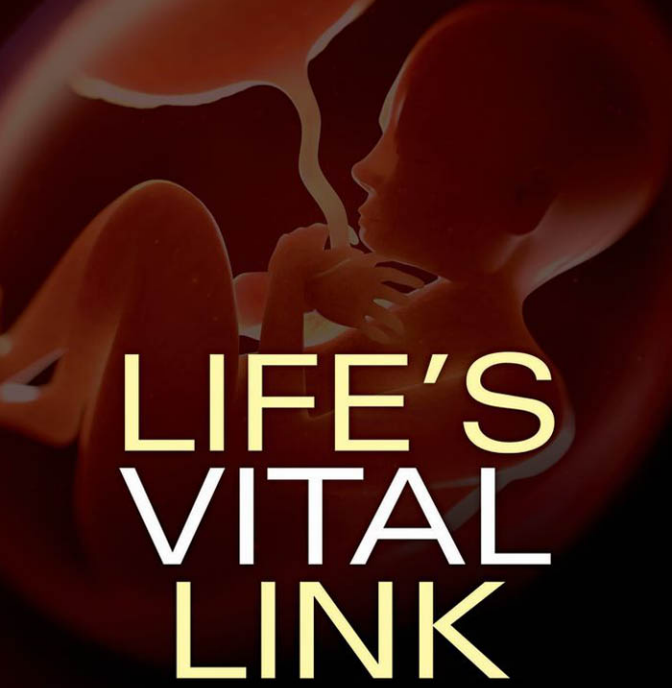

LIFE'S VITAL LINK

the astonishing role of the placenta

Y. W. LOKE

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For all who have touched my life.
'No man is an island.' John Donne

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Author's Notes

Throughout my academic career, all my publications have been directed at fellow scientists. I never attempted to cross the divide from scientific literature to popular science. Now that I have retired from active research, I thought this might be an opportune moment to write for a wider audience, especially as the placenta is a subject that has yet to capture the public's attention. It should be a suitable topic for such a venture.

I decided to approach Oxford University Press because I like the intellectual level at which their popular science volumes are pitched. Not being an established figure in this genre, and without the guidance of an agent, I did not know what kind of response to expect. So I was pleasantly surprised to receive an immediate reply from OUP's Senior Commissioning Editor, Latha Menon: 'The idea of a book on the human placenta is an interesting one. Do send me further details.' This was how a vague idea at the back of my mind became reality. It took exactly nine months from my first letter of enquiry to my signing the contract. For a book on the placenta, I take this to be an auspicious omen. Not only did Latha commission the book, the final manuscript has greatly benefitted from her skilful editing. I owe her a double acknowledgement.

Rotraud Hansberger (philosopher) was the first person to view a few preliminary chapters of the book. I wanted to gauge the reaction of a reader who was not a scientist. Her response was so enthusiastic I was persuaded that the project was viable. Barry Keverne (neuroscientist) kindled my interest in the alliance between the placenta

and the brain. Ann Frost (hispanist) kindly polished my grammar. So many people from different areas of reproductive biology have given their valuable time to talk to me that it is not possible to thank them all individually. Their names are featured prominently throughout the book. This should serve as my acknowledgement to them.

Many of the ideas in this book originated from my close research collaboration over many years with Ashley Moffett. While my own interest has been largely focused on the placenta, Ashley's expertise lies with the uterus. Together, we successfully covered both sides of the fetal–maternal relationship.

Sue Griffin devoted many hours to typing the manuscript, right from the beginning when I handed her sheets of seemingly illegible scrawl. Every line in this book represents her fine handiwork. Anne Marie Catchpole helped me compile the endnotes and glossary. All the drawings are by Emily Evans.

This book is for my family. I hope it will give them pleasure.

Contents

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1

After the Afterbirth

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

The baby within the mother's womb is not alone. It has a constant companion throughout pregnancy. This is the placenta. But the placenta is more than just a companion. It has a very important job to do which is to connect the baby with its mother. This link is crucial because the baby's life-support systems are not yet fully functioning at this early stage of development. Meanwhile, it has to 'borrow' whatever it needs from the mother, using the placenta via the umbilical cord like a jump lead to plug into the mother's battery while its own is flat. The placenta brings in oxygen and food from the mother and, at the same time, excretes waste products back to the mother for her to dispose of. It manufactures products vital for sustaining pregnancy and also forms an effective screen which protects the baby from harmful agents coming from the mother. To perform these complex tasks simultaneously requires flawless organization

by the placenta. Even minor disruptions can have serious consequences not only for the baby, but also for the mother.

Yet in spite of being the star of the show, the placenta has never quite managed to gain the attention it deserves. Compared to other organs of the body, the placenta comes very low down the list when measured on the scale of public awareness. It is not the placenta's fault that it has languished in such obscurity. No one has bothered to speak up on its behalf and to put it firmly into the public domain. This book intends to do so. It will trace the life of the placenta from the very moment it is created within a fertilized egg, through its brief but eventful stay within the womb and finally to its ultimate fate after delivery.

It is easy to see why certain organs are inherently fascinating. Take, for example, the eye. How did evolution, even with millions of years at its disposal, manage to design such a complex and intricate structure? Then there is the heart, a piece of muscle that continues to beat uninterrupted for decades. Or the brain with its elusive concepts such as 'reasoning' and 'consciousness' that have kept it at the forefront of the public's imagination. How does the placenta compare with these titans of the anatomical world? In my view, very favourably. The placenta can also lay claim to many exceptional features not found in other organs of the body. These will become apparent as the book unfolds.

Many people do not have a clear idea what the placenta is, let alone what it is for. There is even some confusion as to where it comes from. Is it made by the baby, by the mother, or by both? This question is likely to elicit a wide range of opinions. I know because I have already put it to the test among friends and colleagues. Surprisingly even biologists are uncertain. The answer is that it is derived entirely from the baby but is so closely attached to the mother's womb throughout pregnancy that one can be forgiven for thinking that there must be some maternal contribution to its formation. Hands up all those who answered this question correctly!

Since the placenta goes about its duties so unobtrusively, it is easily overlooked and ignored. While she cradles her newborn infant in her arms, how many mothers would pause for a moment to reflect on the organ that has made it all possible? Very few, I would imagine, for it is not customary to present the mother with her newly delivered baby and placenta at the same time. I hope I am not stepping on too many toes when I say that obstetricians themselves are also not too concerned about the placenta in spite of the fact that many of the problems they have to deal with are the direct result of placental dysfunction. To be fair though, present knowledge about the placenta is not yet at the stage when it can be translated readily into medical practice, so clinicians cannot be blamed for just getting on with the job of treating the patient without paying too much attention to how the placenta might be involved.

Works of art do not normally generate deliberations on the placenta but there is one drawing that deserves closer inspection. Ironically, it was the absence rather than the presence of a placenta that initially provoked an interest in this picture. Leonardo da Vinci, the Renaissance master painter, is credited as the first person to depict the human baby in situ inside the womb using a specimen obtained from a cadaver. This is his renowned figure of the 'fetus *in utero*', completed around 1512, which now hangs in Her Majesty the Queen's collection at Windsor Castle (see Figure 1a).[1] Viewed through the lens of a reproductive biologist rather than an art historian, I would draw the reader's attention to several interesting features in this picture.

Famed for his critical eye for detail in all his anatomical illustrations, Leonardo curiously left out the placenta in this particular drawing. Was this an oversight or was it a deliberate omission because he did not consider the placenta sufficiently important to be featured? Leonardo's subject was estimated to be about seven months gestation age, by which time the placenta should be a prominent aspect of a pregnant uterus (see Figure 1b). Leonardo though

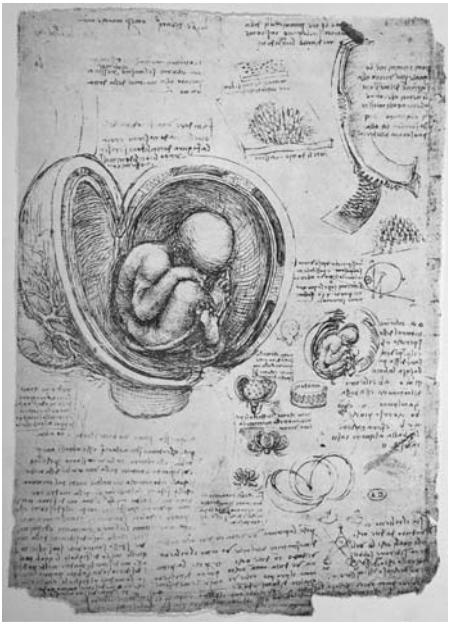

FIGURE 1 The drawing of the fetus *in utero* by Leonardo da Vinci does not include a placenta (a). (Leonardo da Vinci/ The Bridgeman Art Library/ Getty Images).

Compare this with the picture of an actual fetus *in utero* where the placenta is a conspicuous feature (b). Note also the cow's placenta and the plant seed pod in Leonardo's drawing.

did include a separate sketch of a placenta beside the main picture of the fetus *in utero*, but this was taken from a cow's placenta. He couldn't have made a worse choice because, as we shall see in a later chapter, the bovine placenta is one that least resembles a human placenta. Even a mouse placenta, if drawn to scale, will show a better likeness. All this, of course, was in the 16th century. Our knowledge of placental diversity has improved a great deal since then.

Leonardo's third sketch on the same page comparing the human fetus *in utero* to a plant seed in a pod was a brilliant stroke of prescience. He might not have known then how close this analogy is. Many flowering plants possess a structure called an 'endosperm' which functions just like the mammalian placenta to nourish the developing seed. Did Leonardo get the idea from the 11th century legend of *The Lamb of Tartary?* This was a tree growing in the forest of Central Asia whose seed capsule when ripe would open to reveal a little lamb within complete with a white fleece. In addition, a root sprang from the navel of the lamb, tethering it to the ground around which it grazed. This imagery of a creature, part plant, part animal, whose embryo was attached to its source of food by what appeared to be an umbilical cord, would certainly resonate with someone as curious as Leonardo. Alas, this rather wonderful mythical creation was denounced by the botanist Henry Lee in 1887 as nothing more than the early fanciful description of the cotton plant. Like all legends, the borderline between mythology and reality has become blurred with the passage of time.

The reader will notice something odd about the picture of the pregnant or gravid uterus. It shows the placenta lying alongside the baby. Since the placenta is part of the baby, it should be situated inside the baby like all its other organs. Instead, the placenta spends its entire life outside the baby but within another individual, the mother, where it is intimately attached to her womb. This peculiar association between the mother and her placenta can lead to potential conflict. The placenta, being part father like the baby, is genetically

'foreign' to the mother, making it resemble an alien transplant in her womb donated by another individual. By rights, it should be rejected by the mother's immune system like other organ transplants. And yet it is not. Why? This 'immunological paradox of pregnancy' has preoccupied immunologists for well over half a century and still the solution remains tantalizingly beyond reach.[2] If only we could find out how Nature does it so successfully during pregnancy, we might be able to use this knowledge to prolong the survival of transplanted organs. This potential clinical application is what drives research in this area besides inherent biological curiosity. It is only recently that we have started to question whether this analogy between the placenta and an organ transplant is truly justified. Yes, there are similarities, but there are also subtle differences between the two that cannot be readily reconciled. It is these differences that make the study of placental immunology so fascinating.

The mother tolerates the intrusion of the placenta remarkably well and a sort of truce is usually maintained, although not always as will be revealed in subsequent chapters. This normally peaceful co-existence between placenta and mother throughout pregnancy is one of the most extraordinary phenomena in reproductive biology. Remember that the baby itself is not attached to the uterine wall in spite of taking up much of the space inside the uterus. It lies loose within the cavity. It is the placenta that connects the baby to the mother at the site of implantation, so how the mother 'sees' her placenta rather than her baby is what determines the outcome of her pregnancy. We would do well to bear in mind this distinctive anatomical feature whenever we think about the fetal–maternal relationship. The placenta lies in between.

Nature is clever in designing the placenta to be outside the baby. In the uterus, the placenta occupies a position midway between the baby and mother, in a kind of 'no-man's land'. There is a purpose to this anatomical location. From this position the placenta is well placed to monitor and regulate all communications between mother

and baby. It effectively acts as a gateway controlling what passes through. It transfers oxygen and nutrients from mother to baby and returns carbon dioxide and waste products in the reverse direction, thereby acting as the baby's lungs, kidneys, and digestive tract all at the same time throughout pregnancy. This is not all. The pregnant mother, like everyone else, is susceptible to diseases and yet, with a few notable exceptions, intrauterine infections affecting the fetus are uncommon. This is because the placenta is very efficient in screening out pathogenic organisms, but not all—some pathogens have cleverly devised strategies that can bypass the placental defence.[3] The constant sparring between host and pathogen to see who gets the upper hand is never ending. The remarkable property of the placental gateway is that it is not just an inert filter but is actively selective, encouraging the passage of substances that are beneficial to the baby while barring those that are potentially harmful.[4] It is a very sophisticated piece of machinery that has taken millennia to design. But it is not perfect. Nature, like even the best craftsman, can make mistakes. There are presently a few residual flaws in the model that allow unwanted side effects to creep in, as we shall see later. The tragic saga of Henry VIII and his wives is one such example. The placental barrier is also more porous than we thought, allowing the exchange of cells between mother and fetus. Remarkably, these cells can survive indefinitely in their new hosts.[5] All of us, therefore, are chimeras, harbouring cells within us that are not our own. The view we have of ourselves as distinct individuals may need to be modified.

Being positioned between the baby and mother has a further advantage; it allows the placenta to serve both individuals at the same time. No other organ in the body is required to perform this kind of dual function. We have already noted how the placenta serves the baby. For the mother, the placenta manufactures a variety of products that not only enable her to maintain her pregnancy, but also prepare her for events after birth, such as milk production and care

of the young.[6] The human neonate is relatively helpless compared to some animal species where the offspring is already 'up and running' at birth. Postnatal maternal care is crucial for the survival of the young and is particularly well developed in primates, especially in humans. This nurturing behaviour is the result of placental hormones acting on the mother's brain.[7] Sarah Blaffer Hrdy in her book *Mothers and Others* proposes that this propensity to nurture the young was subsequently extended to the care of animals. This started Man's domestication of animals.

The relationship between the placenta and the brain is much closer than we might imagine, as the reader will see in later chapters. Several imprinted genes expressed in the placenta are also seen in the brain so that development of the two organs comes under the same genetic control.[8] Many placental hormones share structural characteristics with those made by the brain, indicating that they have evolved from an identical ancestral molecule. A further point worthy of attention is that the mother's brain can be affected by the placenta on more than one occasion. The first is when she herself is growing inside her mother's womb at the same time as when her own placenta is also developing. Later in adult life when she becomes pregnant, her brain will come under the influence of the fetal placenta she herself has conceived in her uterus. The association between placenta and brain can span two generations. In this way, the future mother already learns how to respond to placental signals even before she herself is born.

Assembling substances, such as hormones, for our own use is what normally occurs in our body. To make products for use by another person requires a much more complex organization. The latter is what the placenta has to do. For this task the placenta actually co-opts the mother to help. In this way, the baby, via its placenta, manipulates the mother's physiology and behaviour for its own benefit both during and after pregnancy. This is an extraordinary coup by the baby. To do all these things at the same time, the

placenta needs to be an expert in multitasking, which it is. How does the mother feel about having her bodily functions usurped by the placenta? Is she grateful for the help or is she resentful? We shall see.

The events which allow the placenta to form outside the baby begin very early in development, from the moment the egg is fertilized by a sperm.[9] The fertilized egg immediately divides into two distinct populations of cells: embryonic and extraembryonic. The embryonic cells are destined to become the baby proper while the extraembryonic lineage will contribute towards the formation of the placenta. Thus, the fates of the two primitive cell populations are already committed. Over 80 per cent of the cells formed are extraembryonic, which goes to show that creating the placenta is even more critical than designing the embryo. This early separation allows the placenta to pursue and to organize its own programme of development totally independent of the baby. From then on, its life is not influenced by the baby. Indeed, the placenta dominates the life of the baby rather than the other way round. If the baby were to die, the placenta can live on, but not vice versa. Its relatively short existence of approximately 270 days is already pre-programmed right from the start. Its whole life is sped up relative to that of the baby. This placental autonomy holds the key to a successful pregnancy.

Our genetic inheritance comes from both parents. We would expect the genes from father and mother to contribute equally to form the placenta. They do not. In fact, they oppose each other. This is due to an unusual mechanism of gene control known as 'genomic imprinting'.[10] Paternal genes promote growth of the placenta while maternal genes restrain this growth. Without the limiting influence of maternal genes, there would be abnormal overgrowth of the placenta. The corollary is that without paternal genes there would be no placental growth at all. This has been described as parental 'conflict' or 'tug-o-war'. The father wants a big placenta to access the maximum amount of food from the mother to feed the baby, whereas the mother restricts this predatory activity in order to

conserve her resources for the sake of her own health. In every pregnancy there is a struggle between father and mother to gain the upper hand. To have parents argue about who should be in charge of making the placenta seems like a petty domestic quarrel. Biologists are trying to understand the origin of this squabble. The jury is still out as to the reason why it has evolved.

Because genes from both parents are necessary for formation of the placenta, 'parthenogenesis'—development of an egg without fertilization by a sperm—is not possible in mammals, including humans. The example most often quoted as the exception to the rule is the immaculate conception by the Virgin Mary, for she herself confessed, 'how can this be for I know not man?' Furthermore, Jesus is male, and it is difficult to explain how this might have arisen from a parthenogenic conception because eggs only have the female X chromosome. Whether all this is due to divine intervention or has a biological explanation I will leave for others to decide. Noah, at least, had the foresight to recruit pairs of animals rather than singletons into his Ark. There is also the French aristocrat, Madeleine d'Auvermont, who in 1637 found herself in the unenviable position of having to explain how she could have given birth to a son in spite of her husband being away for four years. She claimed that her longing for her husband was so intense that she managed to conceive just by imagining he was with her. Her answer was accepted by the authorities and her son was declared to be legitimate. There is, of course, a more prosaic explanation than parthenogenetic conception, but let's not spoil her story. Conception by sperm alone without an egg is also a non-starter. In the story by Euripides (484 BC) Jason, in the midst of his marital problems, lamented to his wife Medea that life would be much better if men were able to conceive without the aid of women. This, of course, is biological wishful thinking, although there was a time not so very long ago when it was thought that a preformed

baby, the 'homunculus' (Latin = little human) already existed in each individual sperm.

The term 'placenta' was first used by Realdus Columbus in his book *De Re Anatomica* published in 1559.[11] Until then there was no specific name for it and it was simply called the 'afterbirth'. Description of this 'afterbirth' was already well documented in ancient literature, including the Old Testament where it was referred to as the 'Seat of the Soul' or the 'Bundle of Life'. 'Placenta' is a Latin word derived from the Greek '*placous*', meaning a flat plate or flat cake. The anatomical term is 'discoid' because of its shape (see Figure 2). This is a description of the human placenta. Placentas from other animals come in a variety of shapes and sizes. This is where Leonardo made his mistake. Some animals have multiple placentas scattered all over the uterus while others have a circular placenta that spreads round the whole of the inside of the uterus. This variation is, in itself, rather intriguing and has been a source of constant fascination for comparative anatomists and evolutionary biologists.[12] Why has

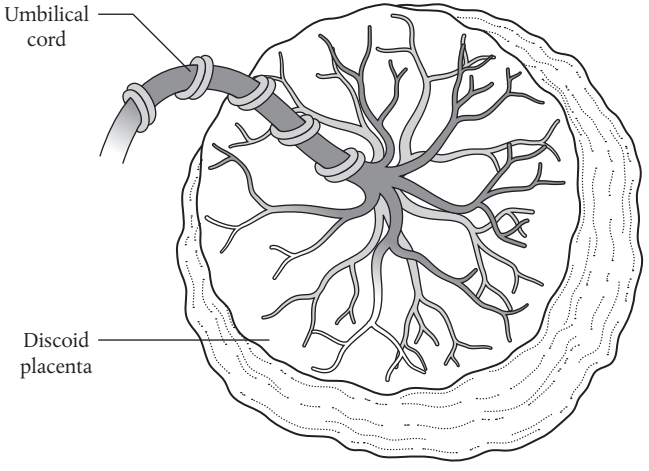

FIGURE 2 The 'flat cake' or discoid human placenta.

Nature played so many enigma variations on the theme of placental diversity? We still do not have a clear explanation for this curious finding since all other organs in the body are, more or less, the same in form and function throughout the animal kingdom. We mammals seem to breathe in air, digest food, and excrete waste products using very similar types of organs, but the way we nurture our young in the womb is vastly different. Why? What are the selective forces in evolution that might have led to each species developing its own type of placenta?

The environment must play a dominant role. Since reproductive fitness is vital for survival of the species, it is imperative that constant and rapid adaptation be made to the design of the placenta to keep pace with changes in habitat. Those species that do not adapt face extinction. As the Red Queen said to Alice in *Through the Looking Glass*, 'it takes all the running you can do to keep in the same place'. Evolution, however, does not follow any specific direction. There is a lot of trial and error strewn with blind alleys. The varied placental types we see now in present-day animals could be the result of this random progression. Characteristics which conferred a slight advantage in a particular environmental niche would be preferred and retained, while others were discarded.

Compared to other mammals, the human placenta is the most intrusive to the mother, penetrating deep into the lining of her womb and even destroying her blood vessels along the way in its quest to obtain the optimum supply of nutrients for the baby.[13] This kind of aggressive behaviour is usually only associated with cancer. Besides invasiveness, the placenta shares many other characteristics with cancer as we shall see in later chapters. This resemblance invites speculation as to the nature of cancer itself. The question is not so much why the placenta behaves like cancer but why cancer behaves like the placenta. The genes operating in the placenta during pregnancy are normally switched off in other cells of the body. Is cancer, then, an inappropriate switching on of these placental genes

in other organs at the wrong time and place? If so, who has pulled the switch? Has this occurred by chance or are cancer cells doing this on purpose in order to imitate the survival tactics used by the placenta? These are all questions posed by both cancer biologists and placental biologists but coming from opposite directions.

Because of the aggressive nature of the human placenta, the mother needs to make some adjustments to accommodate it. We cannot view the placenta in isolation without including the mother's side of the story. She copes by transforming the inner lining of her pregnant uterus into a specialized layer which is able to regulate the activity of the placenta.[14] This layer has to perform two opposing functions simultaneously. It has to restrain the placenta from penetrating too deeply into the substance of the uterus, leading to serious obstetrical problems. But at the same time it must allow some degree of invasion, otherwise the placenta cannot implant properly. The balance between acceptance or rejection is a delicate one. Excessive placental invasion is bad but so is too little. Inadequate invasion will not allow the placenta to access enough nutrients from the mother to sustain its own development as well as that of the fetus. This leads to important pregnancy diseases, such as miscarriage, intrauterine growth restriction, and pre-eclampsia. Furthermore, if the baby manages to survive, the legacy of malnutrition *in utero* will linger on into adulthood when it becomes highly susceptible to a variety of diseases, a phenomenon known as 'fetal programming'. Experience in the womb can affect the whole future well-being of an individual. This offers a new insight into life before birth.

Human placentation is a highly dangerous process, inclined to myriad complications. Other species make do with a simpler and less invasive kind of placenta that is not so risky. With humans appearing so late in the evolutionary tree, it is pertinent to ask why we have not upgraded to a better placental model. Is the human placenta already so well designed that no further modification is needed or are we trapped in an out-of-date model from which there is no

escape? Has development of the human placenta reached a cul-de-sac? Indeed, human reproduction is altogether not very efficient. This might be a paradoxical statement to make in view of the population explosion worldwide. It should be pointed out though, that this increase is due more to a fall in mortality than to a rise in reproductive success.

I have studied the human placenta for most of my academic career and over the years have come to look upon it with increasing awe and wonderment. The formation of the placenta is, without doubt, a significant turning point in human evolution. Without the placenta, the whole course of human history might have been different. For a start we would still be laying eggs instead of giving birth to live babies.[15] The long and tortuous evolutionary road which led from egg-laying reptiles to present-day placental mammals like ourselves was an epic journey spanning over 300 million years. Some species did not complete the journey but branched off at various time points along the way. Two such groups, the Monotremes[16] and Marsupials[17] are still with us today. These creatures are immensely interesting because they provide us with a glimpse into the past as to how we ourselves might have reproduced if we had not continued along the route towards developing a placenta. But apart from these two exceptions all present-day mammals, including humans, belong to the Eutherians, whose hallmark is the presence of a well-developed placenta. The widespread adoption of the placental mode of reproduction is compelling evidence for the advantages it must confer, otherwise evolution would not have encouraged its development. As we saw earlier, even flowering plants have decided that the development of a placenta-like endosperm to nourish the growing seed is the best way forward. For members of two such distinct kingdoms, such as plants and animals, to hit on the same idea is a classic example of convergent evolution.

Choosing the right way to reproduce that best fits with environmental conditions is the most important factor in sustaining the

continuity of a species. The phrase 'survival of the fittest' was originally attributed to Darwin's evolutionary theory but was, in fact, coined by the social philosopher Herbert Spencer in 1864. It has often been criticized for harbouring elitist connotations that are somewhat distasteful. But to biologists, the term fitness refers simply to reproductive fitness. There are no social or moral overtones. Those who are most efficient in breeding will win the evolutionary race. They will add to the gene pool and the species will live on. Reproductive success takes precedence over everything, including the fight for survival. Indeed, if breeding and survival were to come into conflict, it is generally the latter that will be sacrificed. Take, for example, the peacock's tail, where the attraction of a mate has priority over the unwanted attention of a predator. A beautiful and conspicuous tail is a double-edged sword. Advertising can be harmful to health but the peacock is willing to take the chance. For him, sexual triumph is paramount. While the male struts and preens, it is the female who will choose because she is the one who will make the major commitment in time and resources throughout pregnancy. Robert Trivers in 1972 formulated the theory of parental investment and, in mammals, the female invests more heavily than the male for each offspring. In so doing, she becomes the driving force behind the evolutionary process.

The exciting thing about placental research is that it touches on issues beyond reproduction. The placenta shares many features with organ transplants and also with cancer, two other major unsolved biological mysteries of today. A common thread links their natural history. If we succeed in understanding one, we should be able to understand the others.

2

In the Beginning

Soon after our planet was first formed around 4.6 billion years ago, its surface was almost entirely covered with water. Even today, Earth remains a 'water' planet. The continents are dwarfed by vast tracts of ocean which is clearly evident when Earth is seen from space. And this does not include all the water hidden beneath the surface. It is not surprising then, that all forms of life started in the sea, from simple unicellular organisms like bacteria to more complex multicellular ones from which we are all descended. Preserving this aquatic legacy, the human baby continues to be cocooned in 'a bag of water', the amniotic sac, throughout its life in the womb.

Amphibians arrived on the scene during the Devonian period 410–355 million years ago. They were the first group of animals to emerge from the sea and venture on to land. Living examples of amphibians are frogs, toads, salamanders, and newts. But amphibians have not solved all the problems associated with terrestrial life. The major hurdle is reproduction. Although they can live on land, they

are still restricted to life near water because they have to return to water to breed. Frogs' eggs for example, have a clear jelly-like coating which is susceptible to drying and their young larvae (tadpoles) which hatch from the eggs can only survive in water because they pass through an aquatic phase in their development when they have fish-like gills for breathing.

Following on from the amphibians came the reptiles, who had two major inventions which eliminated reliance on open water for reproduction. The first of these was the development of sexual organs by the male that could deliver sperm directly into the female's body, a process known as intromission, rather than just scattering them into the surrounding water as amphibians do. This saves a lot of wastage of sperm and increases the opportunity for a sperm to meet up with an egg. Fertilization inside the female becomes less chancy. The environment inside the female reproductive tract is also more suitable for sperm survival compared to outside. Another advantage of internal over external fertilization is that, in the latter, the coating around the egg has to be a compromise between offering protection for the egg while at the same time still permitting the entry of sperm, whereas in the former the egg coat can be added after sperm has penetrated. There is then no longer any constraint on the thickness or composition of the eggshell.

The second innovation which distinguishes reptiles from fishes and amphibians is the production of the 'amniote' or 'cleidoic' (enclosed) egg by the female. In this new type of egg, the embryo is independent of its surroundings, protected by an eggshell that can prevent desiccation but is sufficiently porous to allow gaseous exchange. Getting rid of waste products is more problematic. Fishes and amphibians excrete their waste nitrogen products as urea. This substance is highly toxic but is very soluble so will rapidly diffuse away in the large volume of water surrounding the eggs of these species. But for an embryo inside a cleidoic egg to produce urea would