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Shaping our destiny: genes, environment and their interactions

This book is about a set of biological responses we have termed *predictive adaptive responses*, and their implications for understanding evolutionary processes, health and disease. These concepts flow from our more recent insights into one of the oldest debates in biological science.

Since the time of Hippocrates, there has been discussion about which characteristics are primarily genetic in origin, and thus immutable, and those characteristics that are plastic in nature, and thus can be influenced by the environment. The impact of modern molecular, genomic and developmental biology on our capacity to understand and address the issues that arise from this big question has been enormous – it is that explosion of biological understanding in the last 30 years that underpins this book. But as we have eradicated many causes of premature death, at least in the developed world, we have become much more conscious of the ongoing impact of environmental influences. In the enthusiasm for modern genetics, this has been much less studied. Yet it is critical we understand that it is the *interaction* between our environment and our genes that determines our destiny. It is now naïve to think about genes (nature) and environment (nurture) in a dichotomous way. We now comprehend that the manner in which the environment affects gene expression on one hand, and how genetic variation affects the response to the environment on the other, is the basis of biological destiny.[1]

However there is a newly emerging dimension to our understanding – namely that the interactions between genes and environment very early in life have a predictive role in defining how any subsequent interactions will be resolved. It is the nature of those predictive interactions early in life and their consequences that is the real focus of this book.

[1] This is well illustrated in the title of the book by Matt Ridley, *Nature via Nurture* (New York, NY: HarperCollins Publishers Inc., 2003).

In the early chapters of the book we examine how genes and environment interact to control our development.[2] We look at the relative roles of genes and environment, and we start to ask the questions of when and why these interactions occur, and what are the consequences – not just the immediate consequences at the time of the interaction, but consequences for the entire life history of the individual. It is the answers to these questions that led us to the formulation of the concept of predictive adaptive responses. But first let us use some comparative biological and human examples in order to illustrate what we really mean by gene–environment interactions.

Lessons from the Antipodes

Australia was colonised relatively late in British colonial history. A penal colony was established at Botany Bay in 1788, but soon afterwards organised colonisation of this vast continent by working class British people wishing to improve their lot was encouraged. Rather than moulding to their new environment, the settlers tried to reproduce their familiar environment within the new colony. Many plants, birds and animals were brought to the new land. One food source these settlers could not do without was rabbits! After several failed introductions, 24 wild rabbits from the English countryside arrived in Australia aboard ship in 1859 and were successfully released.[3] The rabbit population increased far more rapidly than did the human population, as they had few natural predators and little competition for food. They spread across the continent to occupy a wide variety of environmental conditions, from lush farmland to semi-desert, and at sea level and in the mountains. As is well known, they rapidly became pests of such proportions that shooting or trapping them was inadequate, and Australia had to resort to creating hundreds of miles of fencing, and then to biological warfare (by introducing myxomatosis and, when that failed, the rabbit *calicivirus*) in an attempt to control the rabbit pest. What had seemed like a good idea initially became a nightmare, and the success of the Australian rabbits is an often-quoted example of the perils of interfering in a natural environment. No one had realised the tremendous ability of the rabbits to adapt to their new environment and to multiply accordingly. The Australian farmers expected the rabbit population to be no more extensive, and no more of a nuisance, than on a nineteenth-century English farm. But this unfortunate and unintended experiment with nature provides us with an insight into biological adaptability.

[2] Those readers with a working knowledge of genetics, developmental biology and evolutionary theory may prefer to skip chapters 1 and 2.
[3] It is thought that the rabbits were introduced as food for foxes, which were also introduced by the settlers. The problems of the British passion for fox-hunting are still debated today!

It turns out that, despite the originally homogeneous stock of rabbits brought to Australia, they are now very diverse in appearance. Throughout the country they vary in size and shape, body-fat content, coat colour and even in enzyme biochemistry. Research on body shape has revealed some intriguing differences. Rabbits born in the hotter and more arid parts of the country have less body fat than those living in the cooler regions. This is a very helpful adaptation because the insulating properties of fat are reduced in the hot climate, and increased in the cooler climate. Apart from body insulation, rabbits regulate body temperature by active means, and an important mechanism utilises the extensive blood supply to their ears, because when they are hot they can increase this blood flow in order to lose more heat, and, when cold, the flow can be reduced. Interestingly, it turns out that rabbits living in the arid parts of Australia have longer ears than those from the cooler climes.

How could such consistent changes in ear length and body fatness have arisen? Clearly they are appropriate adaptations to the environment. Presumably ear length is influenced by multiple genes, and in each generation different profiles of gene expression[4] will lead to some variation in ear length. If there were no survival advantage related to ear length then there would be no difference in ear length between rabbits from different geographical regions. However, in the hotter climates the animals with variation favouring longer ears survived better and thus were more effective reproducers; gradually ear length evolved to be longer in the hotter regions. This is a classic example of how genes and environment have interacted over time to produce two breeds of rabbit with different characteristics that confer a relative advantage or disadvantage in a particular environment. This is evolution in action within a species, producing population or group diversity. Animal breeders do this all the time – although in this case the environmental selection is not passive (that advantage comes to the animals because they can survive in the environment more easily) but is active and driven by the breeder.[5]

For many years after Darwin first proposed that the dual processes of natural and sexual selection drove the change in structure of organisms and ultimately led to new species formation, there was much doubt that selection could explain adaptation, because it was generally believed that these changes would be too imperceptible between generations. Then in the 1970s biologists returned to the Galapagos Islands, the source of many of Darwin's insights, and observed how the finch's beak changed

[4] Gene expression is a technical term referring to when a gene is active because it is being actively transcribed by the cellular systems to initiate formation of RNA, which in turn initiates specific protein synthesis. Genes are activated and turned off in a complex regulatory framework within a cell – they need not be fully on or off. Thus genes can be highly active with high rates of expression or conversely have low rates of expression.

[5] The success of selective breeding is related to the genetic determinants of the traits of interest. The fewer genes, the easier the selection. If a characteristic is not genetically determined it cannot be selected for. That is why racehorse breeding is such an uncertain business!

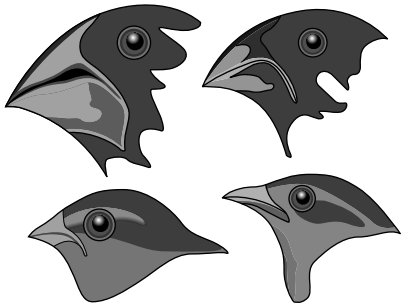

Fig. 1.1 Within a species, variations in phenotype can confer a survival advantage in a given environment, or in the face of an environmental change. The beaks of one species of finch in the Galapagos Islands are a good example. They were instrumental in the development of the theory of natural selection by Darwin. Redrawn from F. J. Sulloway. *Journal of The History of Biology* **15** (1985), 1–53.

in a *single* generation in response to drought. Much to their surprise they found that a single episode of drought was sufficient to cause a 5 per cent change in beak size – because the deepest beaks were best for attacking the tough seeds that survived the drought. But because more males than females survived the drought, the females became choosy about their mates, and the successful males were those that had the largest and the deepest beaks. They therefore had more progeny. So sexual selection added to natural selection: the next generation also had 5 per cent deeper beaks than their immediate ancestors. But after it rained it was the young finches with the smaller beaks that were more likely to survive, because juveniles were more able to eat soft seeds. The influence of selection became diluted and lost after the rains (see Figure 1.1).

So there are tensions in selection processes. Environmentally-induced shifts in appearance (phenotype) only stabilise when the environment is permanently shifted in one direction or another. As we shall see, much of this book concerns the reality that individuals do not develop in a stable or uni-directionally changing environment – but more about that after we define what we mean by 'environment'.

Evidence of gene–environmental interactions in development: a brief comparative anthology

Yellow dung fly are spread worldwide. Females lay their eggs within cattle dung on which the hatched larvae feed. The most important environmental influence for the dung fly is therefore the amount of cattle dung available! Where there is a limited supply of dung, there will be competition for laying sites between dung flies within one species and between species. To deal with this, the developing insects accelerate

their maturation and mature at a smaller body size – in other words they 'trade off' growth to reproduce. When dung is readily available, they grow larger and take longer to mature. The entire life cycle of growth, development and reproduction of the dung fly has been changed by the temporary environment of the larvae.

Similar environmentally-induced developmental changes are found in various locusts and grasshoppers. Many locust species respond to overcrowding and shortage of food by migrating. But to migrate they have to change their body form and their metabolism. Their wing shape and size must be different to fly long distances and they need to use fat as a high-energy fuel to migrate over long distances. They also need to be able to eat a wider range of plants. But these changes, while determined in the larval stage, only have their importance once the locust is fully developed. So this poses an interesting and fundamental question – are decisions made in early life that relate to the ability to survive in later life? There is an obvious advantage to the locust in an overcrowded situation in being able to fly away to a new source of food. It is thought that the larvae detect chemical signals (pheromones), which induce such morphogenic changes and a variety of other morphogenic changes to create body form and function appropriate to migration, rather than the alternate sedentary form. They also use a change in body colour to signal the change to other locusts, and indeed to predators (see Figure 1.2).

These two examples, both involving insects, show that environmental influences acting early in life can create changes which persist throughout life and have their primary advantage in later life by ensuring the capacity to reproduce. These are examples in evolutionary terms of true adaptations, where an adaptation is defined as a response that can be demonstrated to promote reproductive fitness.

Similarly in some species of reptile and fish, environmental influences can have a profound and permanent effect on the appearance of the animal – namely whether it will be a male or female. Unlike in mammals and birds (where anatomical gender is determined by the different chromosomal arrangements in males and females), in species such as the Mississippi alligator or the green back giant turtle it is the temperature of the incubated egg that determines gender. If the egg clutch is buried in sand in a position that keeps it warmer, the embryonic turtles will be female. If the nests are in a situation leading to cooler eggs, the hatchlings will be male. In alligators it is the other way around! We do not know whether the site of the nest is actively chosen by the mother so as to ensure male or female offspring but the possibility is intriguing.

Can similar phenomena occur in mammals? It has been found that coat thickness in the offspring of the meadow vole depends on the season of their birth: if they are born in the spring their coats are thinner than if they are born in the autumn. Thus their fur coats are appropriate for the climatic conditions that are likely to occur in the months following birth. It is not the temperature at birth that determines coat

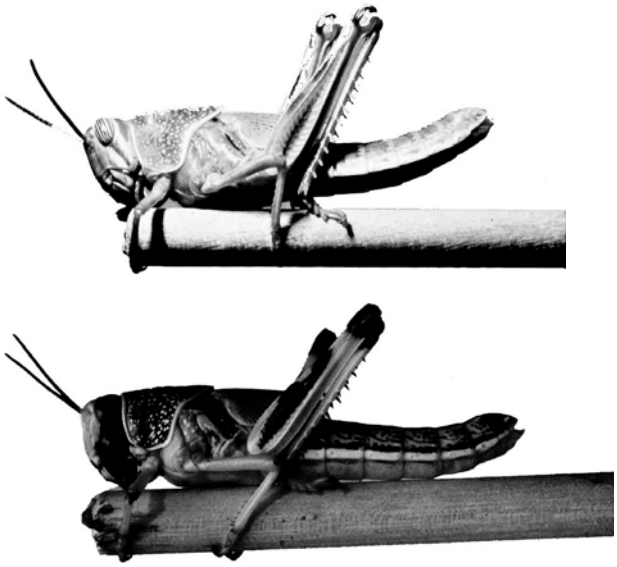

Fig. 1.2 Locusts develop with strikingly different body colours when their population density changes. The so-called 'solitary form' (top) is much lighter than the 'gregarious form' (below), which occurs in juveniles when the population density increases. This precedes swarming and migration, but it also indicates to predators such as lizards that the locust population has reached a point where they may be eating plants containing compounds toxic to the predators. (Photograph courtesy of Professor S. Simpson.)

thickness, because it is roughly the same in spring and autumn. Experiments show that it is hormonal signals from the mother responding to altered day length that determine the offspring's coat thickness while it is still a fetus. The biology of the fetal vole is responding to information from its mother about changing day length and *predicting* the appropriate coat thickness to have in the coming months after leaving the nest. This cannot be solely genetically determined – otherwise all voles born to the same parents would have the same coat length. Information is being processed so that the genes that determine coat thickness change their degree of expression *in expectation of a future environment*, the nature of which is *predicted by some aspect of the current environment.*

Intriguingly, Charles Darwin also touched upon this point in *The Origin of Species by Means of Natural Section*, first published in 1859. In a section on the Laws of Variation, he noted that 'it is well-known to furriers that animals of the same species have thicker and better fur the further north they live; but who can tell how much of this difference may be due to the warmest-clad individuals having been favoured and preserved during many generations, and how much to the action of the severe climate?'. One wonders what he had in mind when he then refers to 'the definitive

action of the conditions of life' and contrasts them with the process of natural selection – was he pre-empting our current discussion?

There is evidence that such environmental interactions also exist in humans. Japan extends over many degrees of latitude. This creates a climatic range from the cold northern islands such as Hokkaido to the sub-tropical southern islands such as Okinawa. When the Japanese army invaded the tropics in 1941 they discovered that heat stroke was more common amongst those soldiers who had been born in the northern islands than in those born in the south. Heat stroke occurred more often because these soldiers could not effectively use one of their key means to reduce body heat – that is sweating – and they simply sweated less than those who adapted well. This led to the discovery that the number of active sweat glands is set soon after birth and does not change through life. But the ability to determine the number of active sweat glands is a once-and-for-all choice in development – once determined it is irreversible and one has to cope with that number of active glands throughout life. It was the number of functional sweat glands that differed between the different groups of soldiers. Those who were born in a cool climate had less active sweat glands and those born in a warm environment had a greater number of active glands. This example also illustrates how a *critical window* in development occurring early in life can have life-long consequences. The number of sweat glands that are set to become active is determined by an adaptation to the local environment at birth, and the choice made at that stage, as a result of a transient gene–environmental interaction determining sweat gland activation, has life-long consequences.

Clearly the number of active sweat glands is not genetically determined. Indeed, examination of the total number of sweat glands in the skin shows that all Japanese have similar numbers – the difference is that some become activated and some do not. This is determined by the degree of innervation of the sweat glands by the sympathetic nervous system. It is the actual environment at a critical period in early development that sets the number of active sweat glands. If this were a genetically determined phenomenon, then over a relatively small number of generations individuals would have the number of active sweat glands determined by their ancestors. But it is obvious that this is a highly adaptive response, making it possible to adjust the number of active sweat glands to a new thermal environment within a generation. Perhaps this high degree of adaptability to differing environments explains why in human prehistory human migrations over long distances could occur rapidly with such success. For example, the Americas appear to have been settled from Alaska to Tierra Del Fuego within a period of perhaps only 1000 years from the initial crossing from Eastern Siberia to Alaska over the Beringa land-bridge. The active sweat gland adaptation is helpful both to the neonate, who also needs to thermoregulate and be able to lose heat, and to the adult – that is, it has

both immediate and long-term advantage. But of course the long-term advantage is only there provided the environment does not change.

The story of the Japanese soldiers demonstrates well how a past adaptation that made sense in one environment can influence one's ability to survive in a new environment. Such examples may seem extreme but, as we will see later in the book, they may be of contemporary relevance to the changing patterns of disease in many countries where nutrition is rapidly shifting from a poor to a relatively rich plane. We must conclude that the genetic make-up of the individual animal or human is not the only factor that determines either its appearance or its capacity to respond to a given environment. And, as we have already seen, there is a strong developmental component to how these interactions are determined.

So the balance between genetic determinants and environmental influences, the so-called gene–environment interaction, is at the heart of both how an individual thrives or does not thrive in any given situation. The deep beak of the finch was advantageous for the adult and disadvantageous for the infant. It was advantageous in a dry environment and disadvantageous in a wet environment. This is an important concept – just because selection has induced an adaptation does not mean that this adaptation will always be advantageous. Perhaps the most obvious example is one first used by the famous geneticist Richard Dawkins in his book *The Extended Phenotype* (see further reading, p. 218). The moth and many other nocturnal insects have evolved with an adaptation to fly towards light – this allows it to escape from a cave. While this makes sense when seeking food, flying into fire or an electric light is a terminal fate for many moths – clearly not, at that final self-immolating moment, an advantageous adaptation! These considerations are found at every level in the biological realm, both plant and animal, and the human cannot be considered differently.

We must now turn our attention to two important definitions: phenotype and genotype.

Phenotype

Phenotype is the term used to describe the actual appearance and function of an individual organism. Most commonly the term is used to describe physical characteristics (for example, tall or short, fat or lean etc.). We will frequently refer to the physical phenotype at birth that encompasses the various measures that can describe size at birth – weight, length, head circumference etc. However, the term *phenotype* is actually more general than just a reference to physical measurements – it extends to include the entire status of the animal or human in physical, functional and biochemical terms. Thus a schizophrenic individual and a person suffering from

depression might be considered to have different personality phenotypes. Similarly a person with high blood-sugar levels due to diabetes and a person with normal blood-sugar levels have different biochemical or metabolic phenotypes. We will use the term *phenotype* in its most generic sense – that is, to describe the sum total of the biochemical, functional and physical characteristics of the animal or human at the point of observation. An obvious question that will appear recurrently throughout this book is 'What determines phenotype?' It is obviously not only the genetic make-up of the individual. Imagine two cloned female calves.[6] They will develop as absolutely identical twins – they have the same *genotype* – that is, they are identical in so far as the genetic information they carry. But imagine that, after birth, one calf is raised on good pasture and is kept well 'drenched' to reduce gut parasite load, and the other is raised on very poor pasture and gets a large intestinal parasite burden. The first calf will grow into a large fat healthy cow with good reproductive performance and a high capacity to make milk – to the farmer's delight. However the second calf will be a 'runt' – it will grow poorly – its mature body size will be smaller, it will have less muscle mass and poorer condition and is likely to be a poor producer of milk and indeed calves. Its destiny is more likely to be sold for pet food early in its life. Thus while these two calves have the same genotypes, they certainly do not have the same adult physical phenotypes, and their destinies will be very different. Furthermore the major determinant of their different destinies was their nutritional and health environment after birth – but more about that later.

Identical twins are essentially the human natural equivalent of the cloning experiment we have just described. At the two- or four-cell stage the fertilised embryo splits and two embryos arise, which then develop into two fetuses – each with the same genotype. Yet identical twins are not identical in every respect. Even if two twins look the same to the less familiar, their mother can always tell them apart, because they have different personalities or slightly different mannerisms or one will be a bit heavier or a bit taller – indeed at birth identical (or *monozygous*) twins seldom have the same birth weights, and they sometimes differ by several hundred grams. These differences in phenotype are usually magnified during life, so that more and more we find it easy to tell them apart. Similarly, their biological destinies will tend to diverge. While if one twin develops adult-onset diabetes mellitus, the other is more likely to do so, this is by no means inevitable. The same is true for heart disease, cancer and so on.

[6] Cloning is an imprecise word because it has several meanings. However the cloning we describe here is the scientifically classical way in which embryos are divided to produce genetically identical offspring. It is based on in vitro fertilisation, then when the embryo has reached the two-cell stage, the two cells are dissected apart under a powerful microscope, without harming either, and they are then transplanted back into the donor mother, when each then fully develops into a calf.

So while there is understandably much interest in the role of genes in determining our fate (and the fate of the cow) it is obvious that genes cannot provide an understanding of everything in life – this is a major message in this book.

Genotype

Genes are a relatively new concept. Darwin guessed that there must be discrete heritable elements and this was established by Mendel in 1865. The term gene was coined by a Danish geneticist, Wilhelm Johannsen, in 1909. It was only in the 1950s that the discovery of the double helix by Watson and Crick explained how genes could replicate, and this introduced the idea of the genetic code embedded within DNA. As is well known, Mendel was a monk who became fascinated by the ways in which characteristics in a species could be passed from one generation to the next. He had started life as a science teacher and his mathematical perspectives allowed him to identify some simple rules from some very complex biology. He was fortunate to become a monk in a monastery where the Abbott was also a committed scientist with interests in selective breeding of apples and sheep! Because Mendel's work was essentially lost for many years, we are left with many gaps in our knowledge of his life. One anecdote suggests that he had to modify his experimental model rather early in his studies, as he first started to examine the characteristics of a rat colony which he bred in the cellars of the monastery at Brno. The monastery apparently did not feel it appropriate for a monk to be engaged in an activity which involved so much sex, and so Mendel changed to the study of peas in the monastery garden. Presumably the Abbott was not aware that sexual reproduction also occurs in plants! For posterity, it was very fortunate that Mendel made the switch of species, for it would have been very hard in the rat to demonstrate inheritance of characteristics in the way that he was able to do in the pea. His studies of green versus yellow characteristics, or smooth versus wrinkled skins are examples of characteristics inherited by single genes that exist in only two forms (or alleles), dominant or recessive.[7]

[7] The concept of dominant or recessive genes comes from Mendel. Assume a gene can exist in one of two forms (alleles) – let us say Y or y, which have their origin in the sequence details of the DNA. As each gene is carried in two copies (one inherited from each parent) there are 4 possible arrangements: YY, yy, yY and Yy depending on the gene inherited from the mother or father – both being Ys in the first case, both ys in the second, and one of each in the last two cases. Let us assume Y makes peas yellow because it causes the peas to express a gene that makes the pigment yellow, but y is an inactive gene that makes no colour. If Y is a dominant gene then the presence of one Y gene will make the pea yellow. So peas with the genetic make up YY or yY or Yy will all be yellow and the yy will be green. If, however, the Y gene is recessive and therefore needs two copies to be fully active and visible, then the YY peas are yellow and the yy peas are green, and the Yy and yY peas are not very yellow, or are green. Note that whether the peas were yellow or green would determine their phenotype; and yellow phenotypes could have a range of genotypes (YY, Yy or yY if Y is dominant, or only YY if Y is recessive).