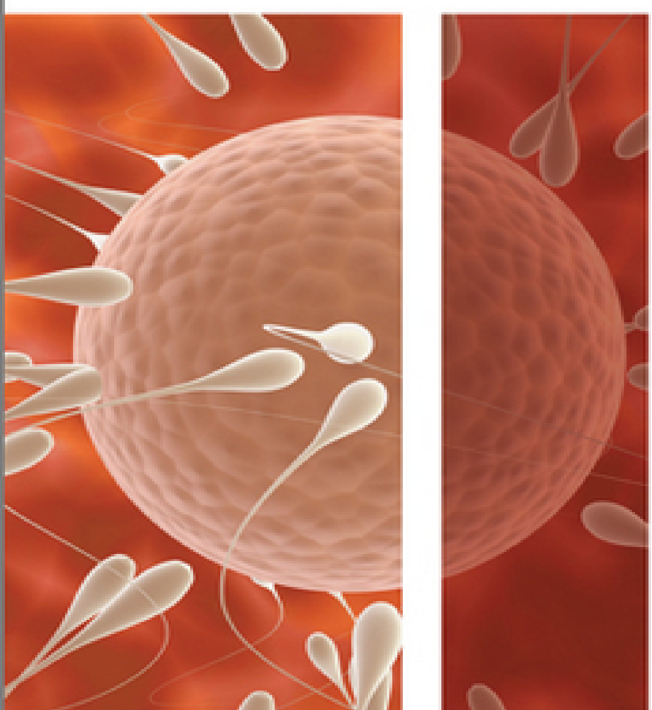
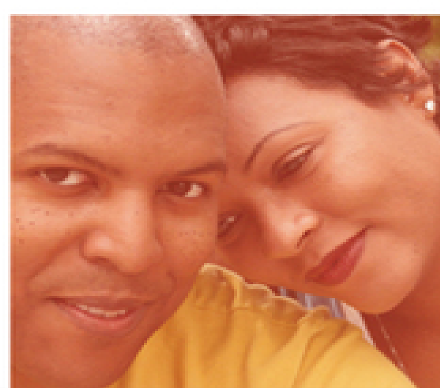
David Lovejoy | Dalia Barsyte

Sex Stress and Reproductive Success





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Contents

Sex, Stress and Reproductive Success

By:

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To our children:
Sabine and Darius

About the Authors

David A. Lovejoy is Professor of Neuroendocrinology in the Department of Cell and Systems Biology at the University of Toronto in Toronto, Canada. Previous to taking his appointment at the University of Toronto he was a Lecturer at the University of Manchester in Manchester, England. He is an author of over seventy scientific publications in the field of reproductive and stress-related physiology and is the author of the book *Neuroendocrinology, An Integrated Approach*.

Dalia Barsyte is currently a senior scientist at the Structural Genomics Consortium at the University of Toronto and is an author of numerous publications in the field of the molecular biology of stress, cancer and environmental toxicology.

Preface

This book is intended to provide an understanding of how mechanisms of reproduction and stress-related physiology interact to allow organisms to cope and survive in an all-too-frequently hostile environment. Although it is intended for second- and third-year university students, we have tried to make it accessible to the interested reader outside of an academic setting. We have attempted, wherever possible, to provide a clear and basic understanding of the physiological processes being discussed. However, we realize that many readers will not have the background to understand all of the concepts introduced in this book. For this reason we have provided a comprehensive glossary that includes definitions and descriptions of the topics covered.

Our understanding of the impact of stress on reproduction is changing on an almost month-by-month basis. It is not possible to include every theory and advance that has been published. We have tried to provide a foundation for a basic understanding of the effect of stress on reproduction and have introduced new concepts that will probably have a bearing on future studies.

When we first considered writing this book, many of our colleagues encouraged us to discuss the numerous aspects of stress and reproduction across a wide range of all multicellular animals, not to mention those found in fungi and plants. Undoubtedly, the mechanisms of stress on reproduction on invertebrate animals, plants and fungi are very interesting, and in many cases, exotic and unusual by vertebrate standards, but we had to concentrate on a single group of organisms understandable to most readers in order to maintain a focus. Interested readers are encouraged to read and study the mechanisms of stress and reproduction as they will inspire the imagination and study of those biological mechanisms so different from those we typically understand.

We hope that you will find the material covered in this book compelling, but remember that it is only a very small number of species relative to all forms of life on the planet that have been discussed.

Acknowledgements

No book is, of course, the sole result of the authors, and this book is not an exception. Its production is a result of the combined effort of numerous individuals who contributed their time, ideas and resources over the two years we spent writing.

This volume would not have been possible without the support and encouragement of John Wiley and Sons, and their editorial team. In particular, we wish to thank Nicky McGirr who encouraged us to propose the project and was a tireless cheerleader throughout the project, Fiona Woods who kept us organized and on schedule and Celia Carden who handled contract and review details. In addition, we would like to thank Harriet Stewart-Jones, Sarah Karim and Prakash Naorem, for looking after the final edits, galley proof and production details. It is hard to imagine a better team of editors!

The topics covered in this book were the collective result of discussions with numerous colleagues and friends who suggested many of the concepts covered. Professor Robert Dores at the University of Denver provided considerable insight into the evolution of the stress response, Professor Franco Vaccarino and Dr Susan Rotzinger at the University of Toronto spent many hours discussing the relationship of stress with anxiety and depression with us, and Professors Ted Brown and Denise Belsham in the Department of Medicine at the University of Toronto kept us abreast of the latest developments in reproductive physiology. We owe special thanks to Professor Dr Jackson Bittencourt at the University of Sao Paulo and Dr Jean-Michel Aubry at the University of Geneva Medical School for their ideas and understanding of the neurobiology of stress.

We owe a great debt of gratitude to Dr Ian Dunn at the Roslin Institute and Dr Kevin O'Byrne at King's College, London for critically reviewing an earlier draft of this manuscript. Their experience, insight and suggestions had a huge impact on this book.

Completion of this book would not have been possible without the understanding and hard work of the graduate students and research associates in the laboratory: Dr Claudio Casatti, Laura Tan, Dhan Chand, Tiffany Ng, Lifang Song and Tanya Nock. Without them, we could have never found the time to write this book.

And we especially thank John, Natalie, Gillian, Rachel, Paul and Tammy at the ‘Harbord House’ in Toronto, who kept us plied with nutrients while we composed a significant part of these writings. You guys are the best!

Chapter 1

Reproduction Under Safe Conditions

When two great forces oppose each other, the victory will go to the one that knows how to yield.

Lao-Tzu, Tao te Ching (sixth century BC)

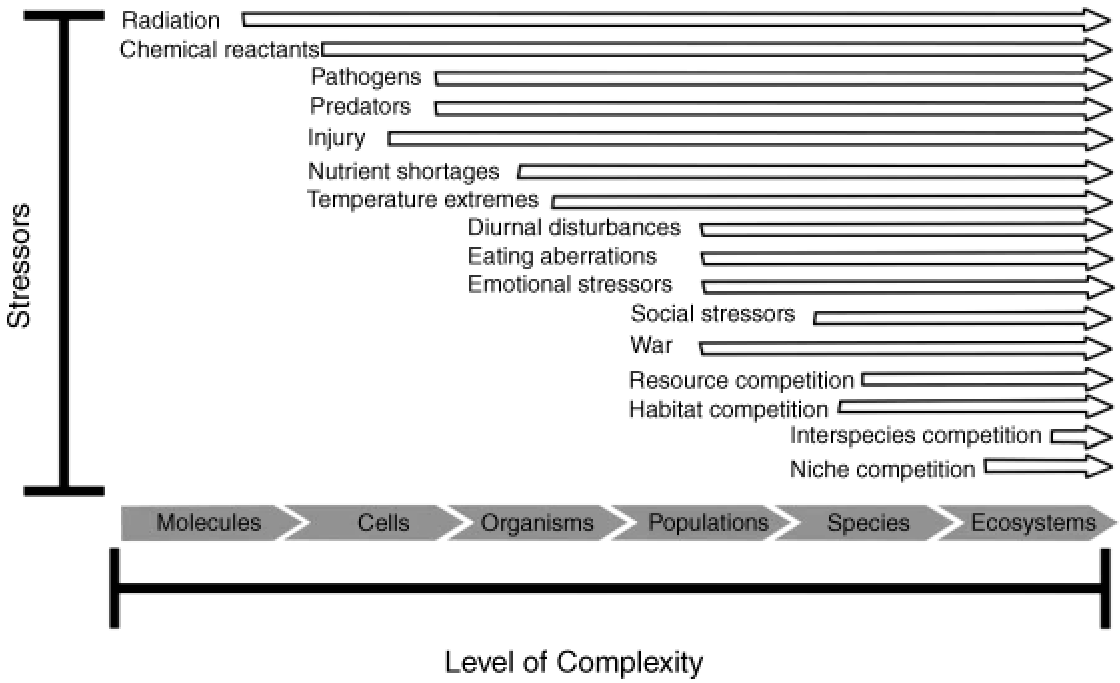
1.1 Introduction

Most of us regard the act of reproduction as a rather private affair. Despite the volumes of books and magazine articles written on sex and reproduction, and its acceptance into public consciousness, we feel uncomfortable discussing sex with a crowd around us. Sex is intensely personal. It's difficult to be romantic with a partner at midday on a crowded city bus, at a football game or when your children are running around the house. No, we prefer those moments of peace when we are alone with our partners. We might put on some music, turn down the lights and unplug the telephone. We create an environment in which we feel calm, relaxed and safe. We don't think about why we do these things, it is intuitive and natural. And we certainly don't consider the results of a few billion years of evolution encouraging us to reproduce under safe conditions.

Reproduction is the primary goal of all forms of life. Without the ability to reproduce, there is no life. This aspect defines all life forms regardless of whether it is a bacterium, protozoan, a plant, fungus or animal. There are a multitude of strategies various life forms have adopted to ensure they reproduce. These include fission of single-celled organisms, the budding of a smaller individual from a larger individual or the fusion of cells, which, in the case of sexual reproduction, leads to the development of a new individual. In some cases, a combination of these strategies may be employed. But regardless of the reproductive strategy used, once the new individual is ‘born’, it must survive in a hostile and unforgiving environment long enough for it to reach a stage of maturity at which it too can reproduce. So, if the primary goal of a species is to reproduce, then a secondary imperative of the individual is to survive long enough until it can itself reproduce. Because the time required to reach reproductive maturity for all organisms is much longer than the time required for the act of reproduction, organisms have evolved a number of strategies and mechanisms that allow them to survive the conditions of a harsh environment.

The environment surrounding an organism is dangerous and constantly challenges its ability to survive. There are seasonal and daily temperature fluctuations, and an atmosphere that allows organisms to respire but is toxic in some ways. There is ionizing radiation from the sun and cosmos. There are mechanical threats in the form of geologic activity, severe weather, wave action, shifting sand and wind. Food sources may be plentiful at some times, but unavailable at other times. And while you, the organism, is trying to survive, other organisms may be interested in attacking you – either larger predators looking for a meal or much smaller ones which cause a variety of diseases. Added to these stressors are the toxins and noxious chemicals that are found in all environments from a variety of sources. We call these aspects that threaten our survival, ‘stress’ (Figure 1.1).

Figure 1.1 Types of stressors that act on various levels of biological complexity. The arrow associated with each stressor indicates the range of complexity that it can affect



One of the fundamental principles of the life history of any organism is that the evolution of fitness-related traits will be constrained by the presence of trade-offs between them. In other words, a beneficial effect on one physiological system can have a negative effect on the expression of another. If we were to consider this with respect to reproduction and stress, an organism could increase its reproductive capacity with a reduced ability to ward off stressful challenges or it could improve its ability to handle stress but with a reduced reproductive capacity. Therefore, for most species there is a compromise that provides a certain level of reproductive capacity with an appropriate level of a stress response that is designed to meet most, but not all, of the challenges for that species.

1.2 What is Stress?

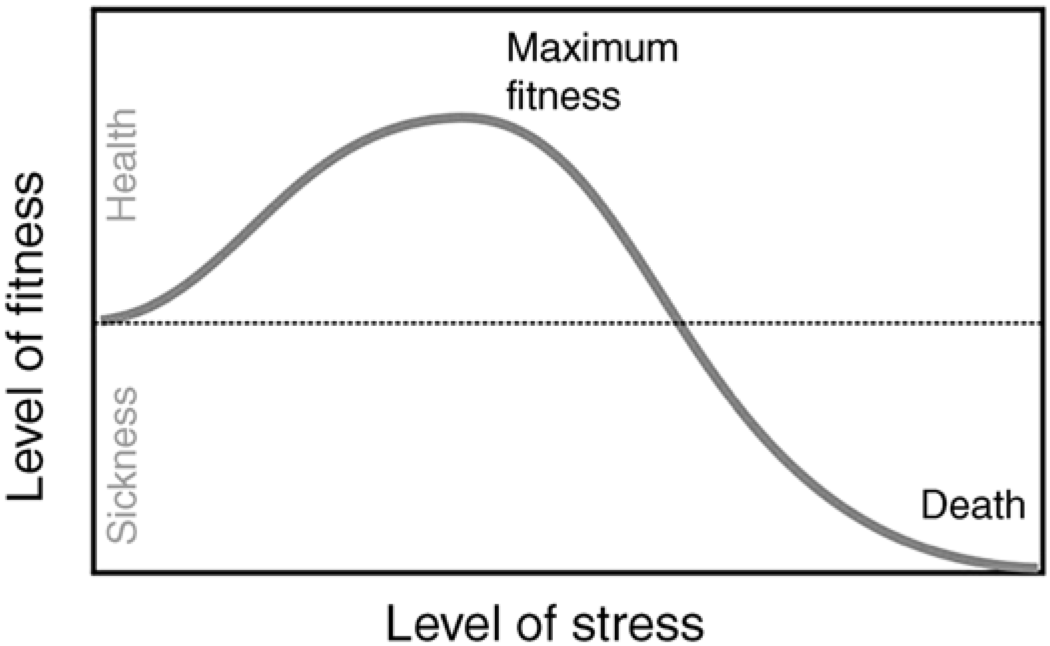
Most of us have an intuitive understanding of what constitutes ‘stress’. For those of us living in an urbanized civilization, most of what we consider as ‘stress’, we experience with psychological and social interactions. We face many of the same problems as other animals as well as others that are unique to our species, such as loss of employment, overwork, too many bills and traffic conditions, to name a few. Under normal circumstances, these stressors rarely bother us, but when these events stop us from carrying out our day-to-day activities, we recognize these events as stress. When stress occurs over a long period of time, we might experience anxiety, depression and a variety of other conditions such as post-traumatic stress disorder, panic disorder or various phobias. Then if an additional stressful situation occurs, medical treatment might be required. In our Western style of living, we have a culture based around the stress of living. A quick perusal through newspaper and magazine advertisements will see that the media encourage us to reduce stress by being pampered by spa treatments, take a getaway cruise to a tropical isle or take out golf or gym memberships. The reality is, of course, that we have to indulge in these stress-reducing activities within the confines of the free time allotted to us and within our financial budgets. For the majority of us, both time and money are limited. Excessive indulgence in these commercially related stress-reducing activities can cause debt and reduce our time available for work. This struggle to fit relaxation time into our daily lives might even increase our stress load. We strive for a balance in life, but only a very few actually achieve it.

The concept of stress was originally recognized as a condition associated with humans, but as we came to understand more about the physiology of stress, we could see that it could be applied to all species. What we routinely define as stress, in the biological sense, has a long history. Hans Selye (1907–1982), a Hungarian physician and scientist, who later emigrated to Canada, coined the term ‘stress’ to account for a group of similar symptoms in patients who were suffering from seemingly unrelated conditions. He agreed with the findings of the French surgeon, René Lerviche, who in 1934 described a clinical syndrome with similar symptoms which appeared after a wide variety of severe surgical interventions. He called this syndrome *la maladie postopératoire*. This observation was consistent with a set of characteristic changes following exposure to certain drugs, infections, nervous stimuli, trauma and burns, suggesting that, despite the great variety of noxious insults to the body, there was a characteristic response in each case.

Selye borrowed the term ‘stress’ from the physical sciences to describe this phenomenon, although in his later writings he suggested that the term ‘strain’ might have been more appropriate. He speculated that perhaps in all the stresses and strains of life, the body could mount a similar defence mechanism to a specific noxious stimulus. This insight was a major step forward in our understanding of stress. What we understand as stress – a condition that inhibits us from carrying out our normal life – he recognized as the symptoms associated with a defence mechanism that the body elicits in order to combat situations that threaten the health of the individual.

Selye also wrote that some stressful conditions were effective in reducing the severity of other potentially damaging conditions, although he was not the first to recognize this – observations that pain, starvation and fever could actually have curative properties date back to early Greek and Roman times. In other words, some forms of stress could actually improve the health of the organism (Figure 1.2). These observations stimulated further research on 'non-specific therapy' which was hoped could elicit a similar physiological response in the body that would help cure other conditions.

Figure 1.2 Relationship between fitness and stress. Lower levels of stress can increase the fitness of an organism. If the level of stress becomes too high, it becomes damaging to the organism. Fitness is defined as the reproductive capacity of an organism



Intrinsic to an understanding of stress is the concept of 'homeostasis'. The nineteenth-century French physiologist Claude Bernard (1813–1878) recognized the difference between the internal body mechanisms, distinguishing the *milieu interieur* or internal environment from the *milieu exterieur* or external environment, which consisted of all those conditions outside the body that affected an organism's health. The internal environment could be described as the total set of physiological and metabolic reactions that occur within the body. The external environment consists of all processes that occur in nature outside the confines of the body. Bernard wrote that the internal environment had to remain more or less constant despite changes in the external environment in order to maintain life. This ‘steady state’ of the internal environment was later described as ‘homeostasis’ by the American physiologist, Walter Cannon (1871–1945). Homeostasis can be defined as the balance achieved by the total set of metabolic and physiological reactions occurring in the organism. Within the context of these definitions, stress was defined as any event that acted to disturb homeostasis, or disrupt the physiological balance of the steady-state internal environment in the body. Biologically, the ‘stress response’ is the set of all neural and endocrine-associated adaptations that help re-establish homeostasis.

Cannon introduced the term ‘fight or flight’ to describe the decision the organism makes when confronted by a stressor. In a situation where it is possible to remove oneself from the stressor, such as a predator or temperature extremes, for example, ‘flight’ ensues. On the other hand, in the case of disease, injury or predation when escape is not an option, ‘fight’ occurs.

Since its original description, the concept of homeostasis has now been subdivided into two forms: ‘reactive’ and ‘predictive’ homeostasis. Reactive homeostasis occurs in direct response to a homeostasis-challenging event (i.e. stress). An example of this might be the sudden threatening appearance of a predator. Predictive homeostasis, on the other hand, is anticipatory, for example when an animal forages for food and anticipates when a food source will become available. The ability to perceive the arrival of a stressor allows an organism to make the necessary physiological adaptation before the arrival of a stressor so that the animal is ready to defend against the stressor. Ultimately, this increases the survivability of the organism. Think how much easier it is if you know ahead of time you have a major examination coming up instead of your professor surprising you with the exam one morning. It is a similar situation with the stress response. Physiologically, it is more efficient to prepare for an upcoming stress than to mount the appropriate defence in direct response to the challenge.

Later, the term ‘allostasis’ was suggested by Sterling and Eyer (1988) to describe the adaptation of the body to greater challenges such as those brought on by stress. They suggested that an organism might experience greater physiological stability by the exposure to variability in the environment. The greater the range of stressful challenges that an organism can successfully overcome, the greater its ability to confront novel challenges in the future.

Selye speculated that disease results following a prolonged bout of stress because the ability to mount a stress response eventually wanes as a result of depletion of various protective hormones. However, today's evidence indicates, in contrast, that it is over-production of these hormones that produces the symptoms associated with chronic stress. Prolonged activation of the defence systems eventually becomes damaging to the organism. If an organism cannot appropriately initiate a stress response during an acute physical stress, then the consequences can be damaging to the health of the animal. Alternatively, if an organism cannot terminate a stress response at the end of the stress, or if it activates the system too much because of repeated or chronic stressors, stress-related disease may emerge. In other words, a little bit of stress is healthy and too much stress is unhealthy.

In Selye's description of the stress response, he described three stages within the context of what he called the ‘General Adaptation Syndrome’. The ‘alarm reaction’ was the first phase and included the perception of the stressor and the initiation of the stress response. The term ‘alarm reaction’ was coined to indicate that this response represents a ‘call-to-arms’, as he described it, of the body's defence forces. Those events that stimulated the stress response were defined as ‘alarming stimuli’ or stressor agents with an action that was localized and required no important general adaptation adjustments. For example, selectively acting drugs or the amputation of limbs are relatively mild alarming agents even if they maximally stimulate or actually kill limited cell groups. Agents that affect large portions of the body, on the other hand, evoke an intense general adaptation syndrome.

The alarm reaction itself is not necessarily a pathological phenomenon. Stressors might be traumatic to large portions of the body. Here, Selye included haemorrhage, temperature extremes, radiation, electric shock, nervous stimuli including emotions, too much muscular exercise or too much rest, anoxia and asphyxia infection, anaphylactic reactions, general acting drugs and other toxic compounds, diet aberrations such as fasting, overfeeding or dietary deficiencies, diurnal variation or climatic conditions. He also stated that being under or overweight, or having various types of gastrointestinal and menstrual disorders and cardiovascular diseases could be classified as diseases of civilization because they are comparatively uncommon in less urbanized societies. Their development is promoted by food habits and stress inherent in civilized life to which the organismal stress response cannot adequately adjust itself. The level of stress in a technologically advanced urban society may be increasing at a rate faster than that at which humans can adapt genetically to the stressors. Our adaptation to this form of stress comes in the form of behavioural changes and, in some cases, pharmacological interventions.

The second stage of Selye's description of the stress response was the ‘stage of resistance’ which was characterized by an increased resistance to the particular stressor to which the body has been exposed and, in some cases, associated with a decreased resistance to other stimuli. The final stage, the stage of exhaustion, represented the sum of all non-specific reactions in the body that develop as a result of prolonged overexposure to stimuli to which adaptations have been developed but that can no longer be maintained. All organisms have a limit to how long they can tolerate the stressor.

Robert Sapolsky at Stanford University refined the concept of stress by stating that the original definition of a stress must be expanded to include the psychological aspects of anticipation, rational or otherwise, of physical and emotional stress. The fear and anticipation are particularly important in human society because of the emphasis placed on emotions. The possibility of losing one's financial security or the presence of a bully, even when no action has occurred, is enough to stimulate this stress response. There are examples of students dropping out of school or, in extreme cases, even taking their own life before obtaining their final grades because they were convinced they would not get the marks they wanted, even though their fears were unsubstantiated. In a study involving first-time paratroopers it was shown that the greatest increase in certain stress-related hormones in the blood occurred just before the soldiers jumped from the aircraft. The jump itself caused only a small additional increase in these hormones. There was also shown to be a major increase in some hormones the evening before the jump.

1.3 Reproduction and Stress

The physiological processes that regulate reproduction are particularly sensitive to stress. In humans, when sufficiently high levels of stress occur over a prolonged period, women can experience irregular or absent menstrual cycles and men may have reduced sperm counts and impotency. In animals, poor husbandry methods in agricultural or zoo settings can lead to a loss of the ability of animals to mate and breed. It has also been noted that a bout of intense but brief stress can inhibit reproductive processes in the short term, with normal reproductive ability occurring after the stressor has been removed or resolved. In observation of this, Selye wrote ‘Curiously, the ovarian atrophy and infertility due to senescence is delayed in mice temporarily kept on a restricted caloric intake. Here one gains the impression that the interruption of sexual life, due to undernourishment, merely “saved” fertility for a later time.’

The longer the time spent to reach reproductive maturity the greater, the chance that an organism will endure a stressful experience by the time it reaches an age at which it can reproduce. Every organism has a unique set of stressors that relate to its niche and habitat. Jellyfish, for example, have to contend with the ingestion of noxious chemicals and bacteria, temperature extremes and predation, whereas for humans these days, the majority of stressors arrive in the form of social and behavioural interactions. Despite these differences, both species must endure and survive these stressors during the passage from birth to reproduction. Thus, there is an optimal window of time in the organism's development where the health and defence ability is maximized to ensure that reproduction can occur. Sapolsky also considered the role of ageing with respect to the stress response. Ageing can be thought of as a time of decreased capacity to respond appropriately to stressors. The aged organism might require less of the stressor for homeostasis to be disrupted or it may take longer for homeostasis to be re-established. In fact, this is likely one of the evolutionary reasons for menopause in women when the reproductive system is shut down when the body can no longer mount the appropriate stress response to deal with stressors. Chronic stress may accelerate some aspects of the ageing effect. Thus, the time at which an organism reproduces has to be optimized for the shortest possible period to reach full reproductive maturity, in which their health is maximal and they are relatively safe from predators and other stressors.

Gestation extends the critical period required to keep stressors at a minimum. The length of gestation varies greatly among organisms. Generally, larger and more complex organisms have longer gestation periods. Also, animals with lower metabolic rates (e.g. shark) tend to have longer gestation periods and those animals with high metabolic rates (e.g. starling) have shorter ones. The gestation period is critical to the development of viable progeny. It is a time when cells are rapidly dividing and differentiating into new cell types. Proliferation and differentiation can be affected by the amount and quality of the nutrients the mother is ingesting, the presence of stress hormones produced by the mother, infection of foreign pathogens or by the presence of toxic chemicals. Prolonged exposure to stressors during this period can lead to a number of developmental abnormalities by altering the physiology of the developing cells, creating progeny that have impaired health and fitness. In general, success of the progeny and, therefore the population, increases if the developmental period is relatively free from these threats. The longer the gestation period the greater the risk that these problems will occur. In many mammals and birds, however, intense stress experienced by the mother may actually modify the physiology of the fetus and embryo so that, as adults, they are better prepared to deal with stressful challenges. These ‘epigenetic’ effects are discussed in Chapter 7.

1.4 Reproduction, Stress and Energy are Intrinsically Interrelated

In the mid 1960s there was an American television series entitled ‘Star Trek’. It detailed the adventures of a starship and its crew as they explored the galaxy. What I thought was interesting about the spacecraft was how they used energy. There was a finite amount of energy produced by the spacecraft, which they could use for speed and transport, or protective force fields or weapons but not for all. In many episodes, they had to make a decision about what they were going to use this energy for. I always thought of that spacecraft as a living organism in itself. We might also liken this energy trade-off to your monthly budget: all living expenses need to be paid, then the remainder is divided between saving for the future and spending on entertainment and other interests.

All animals have to deal with the same problems. All organisms have to contend with a finite amount of energy. Organisms obtain their energy through food and convert this energy into useful energy-containing molecules available to the body through the oxidation of nutrients generally with oxygen, although sulphur is used in some chemosynthetic organisms. This need to obtain our food from ingestion of nutrient molecules makes us different from photosynthetic organisms, such as plants, some protozoans and symbiotic animals, and gives us a unique set of stressors that are related to food-gathering.

A finite source of energy forces animals to make decisions about how the energy will be spent. The amount of energy animals can take in is dependent on the amount and quality of food sources available to them, the ability to convert those nutrients into a form that the body can utilize, as well as having the time available to obtain those food sources. An adequate supply and access to nutrients is required for optimal health. However, when food is scarce or time is limited, many animals will opt for a more convenient but less nutritious food source. Stress and energy production are intrinsically intertwined. The hormones associated with stress are also associated with energy production. Activation of the stress response will curtail the need to eat and digest, but may increase the stamina and locomotor ability required for foraging. It may also trigger metamorphosis in some tadpoles whose ponds are in danger of drying up. A similar situation applies during long bouts of migration experienced by, for example, salmon, when the excessive energy demands trigger a sufficient stress response to inhibit foraging. Thus, due to both internal and external stressors, the stress response acts, in part, to maximize energy production to ensure the survival of the organism.

1.5 Interaction of Stress and Reproduction

The actions of stress on reproduction act at multiple levels of organization in an organism. We would expect, therefore, that the greater the complexity of the organism the greater the variety of stressors that would affect it. Let us consider how all of these levels of organization become involved in complex organisms such as humans.

Before a stressful stimulus can affect an organism, the stressful event must be perceived (Figure 1.3). For all stressors in the external environment, activation of at least one of the special senses is required. This may include hearing, vision, touch, taste, smell or balance for most mammals. In bats or whales, it may also arise in the form of echo-location, or in fishes that can perceive electrical signals, changes in an electric field may be sufficient to stimulate a stress response. The strength of this signal is magnified if additional senses perceive a stressor. Once, while I was camping in a remote region of western Canada, I heard the sound of something moving through the forest. Wondering what it might be, I went to investigate and was alarmed to discover that the sound was being made by a large black bear. At this point, it became apparent that both the bear and I were alarmed by the appearance of an intruder, and after appropriately considering ‘fight or flight’ decision, we both ran in opposite directions. Thus, after the perception of an event in the external environment, and the subsequent identification of the stimulus as a threat, came the associated response. The first sensory response triggered an investigation, whereas the second led to flight, although both perceptions are stressors.