The Fetal Matrix: Evolution, Development and Disease

New discoveries reveal how crucial interactions that determine our destiny occur before birth, when our genes interact with their environment as the embryo and fetus develop. These processes – in the matrix of the womb – are evolutionary echoes of mechanisms that allowed our hunter–gatherer ancestors to survive. These exciting insights into predictive adaptive responses suggest new ways of protecting the health of the fetus, infant and adult. If inappropriate they can trigger obesity, diabetes and heart disease, formerly thought to result solely from adult lifestyle. The new concepts in this book are crucial to understanding the daunting public health burden in societies undergoing rapid transition from poverty to affluence. They add an important new dimension to evolutionary theory. Synthesising developmental biology, evolutionary history, medical science, public health and social policy, this is a ground-breaking and fascinating account by two of the world's leading pioneers in this important emerging field.

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Time present and time past
Are both perhaps present in time future
And time future contained in time past.

T. S. Eliot, 'Burnt Norton'

māt'rix, n. (pl. –*ices*) womb; place in which thing is developed; formative part of animal organ; mass of rock etc. enclosing gems etc.; (biol.) substance between cells; mould in which type etc. is cast or shaped. [L, f. *mater* mother]

Oxford English Dictionary

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Preface

This is a book about a rapidly developing idea that has very important implications both for evolutionary biology and for medicine and public health. It offers clues to a better understanding of the origins of many diseases and their prevention and also provides additional insights into important biological processes relevant to evolutionary and life-history theory.

Ideas in science do not often develop in a manner that Fleet Street would have us believe. Science is not normally about 'breakthroughs' and brilliant scientific insights springing from nowhere. It is a most unusual event for scientific understanding to arise in the 'Eureka!' mode, where a single scientist has a flash of inspiration, jumps out of his bath and runs down the street screaming with excitement. Imagine the streets of Boston or Oxford if science was really like that!

Most science is in fact rather boring, in that each advance in understanding is made by the painstaking and careful work of scientific teams operating in collaboration and competition (often simultaneously!) with each other. Their observations gradually provide greater insights into a particular field. Therefore scientific progress must be measured by a series of small steps – some experimental and some conceptual. It is most unfortunate that the media-driven perception of science on one hand, and the competitive nature of restricted research funding on the other, force scientists to hype and to present scientific progress as isolated 'Eureka moments'.

Despite this caveat, increases in scientific understanding of a field are not linear but episodic. When there is significant progress it often comes because new technologies have been applied. One such technology has been the use of DNA-related techniques to study gene expression and regulation. In turn this has led to the human genome project that produced the surprising result that we have only about 35 000 genes – not enough to explain the myriad proteins and functions within the body. In turn this led to greater attention to post-genomic regulation and that, in turn, to how environmental factors influence genomic function. Whereas evolutionary theory had originally been developed in the absence of knowledge and

understanding of modern genetics, the robustness of the Darwinian model has been confirmed and extended by this growing knowledge.

Other key technological advances have included a variety of new methods that allow us to study body function non-invasively in increasingly precise ways and even, as we shall see, before birth. They range from all sorts of clever imaging methods, including some – such as CAT scans – that just look at the shape of an organ, to methods such as magnetic resonance spectroscopy that allow molecular functions to be studied in the living animal or human.

In parallel, there have been massive advances in our ability to study the earliest processes of conception, implantation and early embryonic development. A particular focus of this book is on understanding of early life, of the embryo, fetus and newborn. Because of these new reproductive technologies, there has been an explosive increase in our knowledge of this period of life in recent years.

The dominant approach to modern science is the Baconian model of hypothesis-creation and testing. This can emphasise a rather narrow approach to obtaining new information. In it, specific hypotheses are generated that can either be confirmed or refuted experimentally. The experiments are designed to test the idea, and the model is modified in light of the results. So science progresses in a day-to-day manner. Hence, most ideas in science just seem to evolve – no single person is the real inventor – rather multiple groups of researchers converge on a problem, offering thoughts and insights and experimental data, and the theory gradually develops.

But ideas in science are not just about getting new data. New theories or models come from thinking about both old and new data in different ways. New thinking is often more important than new data. While research-funding bodies focus on supporting the generation of new data, often in a very reductionist manner,[1] it is the broader integrated synthesis of new ideas from data across several fields that frequently does most to advance our understanding of biology. Perhaps not surprisingly, when this approach is taken, there can be a shift in thinking of such magnitude that a field of science changes significantly and rapidly. The ideas of natural selection and their role in evolution developed by Darwin and Wallace are a dramatic example of such a revolutionary synthesis. They involved observations in geology, biogeography, palaeontology and taxonomy, and they irreversibly changed how we think about biological processes. Often, as in that case, the data on which the new idea is constructed come from very disparate fields, and the new idea arises from the fortuitous recognition of relevance across domains that do not normally overlap. Charles Darwin's work was not done in isolation – evolutionary thought

[1] A reductionist approach in science is based on the idea that an understanding of how a system works will be gained by breaking it down into its component parts, and then studying them separately. The opposite approach is to take an integrative approach.

had been progressing since the work of his own grandfather, Erasmus. What Darwin (and Wallace) did was firstly to demonstrate that evolution was a fact; secondly that one species could evolve into another; and thirdly to provide mechanistic bases (natural and sexual selection) for these related processes.

This book is about a significant shift in biological thinking. It builds on the work and ideas of both ourselves and others. About 15 years ago, it was first suggested that some adult diseases had their origins partly in fetal life. A raft of experimental work and epidemiological and clinical observation has followed that has led us to a reasonable understanding of the biological processes underpinning this link. But as we have considered comparative perspectives and as developmental biology and evolutionary thinking have converged, we have given greater thought to the broader biological significance of these observations.

When we started to write this book three years ago, our intention was to focus on a description of the data suggesting a role for early development in the origins of disease, and its implications for disease prevention and treatment. However, as we worked together discussing the available data and extending our understanding into broader fields, we recognised an increasing gap between evolutionary thought and human medicine, with neither field sufficiently informing the other. Most evolutionary biology books, especially those with a developmental focus, largely keep away from the human, and from human disease theory. Conversely human biology has become dominated by genomic thinking, and the new paradigms of gene–environment interactions – well accepted in comparative biology – have been little considered. Our research forced us to bridge this gap. As we did so, we recognised that a more general framework is possible for thinking about aspects of early development and its consequences for health, disease and biological theory. We have called this new framework the concept of *predictive adaptive responses*.[2] So now this book has two major intersecting themes – one about general biological processes of responses to the environment during development and one about the developmental origins of disease.

The book derives from three related considerations – *how* do species survive short-term environmental changes, *when* do species make critical adaptive choices and *what* are the implications for human biology. As we shall explain, new insights into the first two questions, coming from diverse sources such as molecular genetics, experimental physiology, clinical medicine and epidemiology, led us to formulate the concept of predictive adaptive responses. The fundamental idea is that early in life, primarily in the embryonic, fetal and perhaps the postnatal period, mammals make irreversible choices in their developmental trajectories – not primarily to deal

[2] What is in a name? While we hesitate to put a catchy name to what indeed is a complex idea with a number of antecedents (see chapter 3), the practicalities of communication require a short and specific name to describe the phenomenon addressed. The rationale for this choice is given in chapter 3.

with the immediacy of their environment at the time when they are making the choice – but rather because they are *predicting* the environment into which they will be born or grow up, and in order to maximise their chance of reproductive success as an adult. Such a model explains how species can survive transient environmental change and it is therefore of broad evolutionary significance. But as we shall see, when put into the human context it also explains the origins of many common diseases including heart disease and Type 2 (or adult onset) diabetes mellitus. In turn, this radically changes our concepts of how and when to intervene in populations to reduce the burden of disease. We will argue for a far greater focus on maternal and fetal health.

This book draws on understandings of different areas of science including evolutionary biology, developmental biology, life-history theory, fetal development and clinical medicine. It describes the recent exciting discoveries that led us to posit this idea. But this is not a book only about theoretical biology, it is also about the practical applications of this idea to prevention of disease and to understanding the ecology of disease across the planet. It has significant implications for those involved in public health policy.

Three major themes are covered: developmental biology and fetal and perinatal physiology; clinical epidemiology; and evolutionary biology. In chapters 1 and 2 we provide a description of how the early phases of life progress in humans and other mammals, of what can influence or affect embryonic and fetal development, and what might be the life-long consequences of the effects of those influences. In chapters 4, 5 and 6 we give a description of how events in early fetal life can impact on later life and, in particular, lead to a greater risk of diseases such as heart disease and diabetes. The implications of this for both the developed and developing worlds are discussed in chapters 9 and 10. The exciting experimental, clinical and epidemiological science underlying the above observations led us to reflect on the significance of why we have evolved mechanisms that operate in early life but that can have adverse consequences in later life. The idea is introduced in chapter 3 and expanded upon in chapters 7 and 8.

One important conclusion is simple: in fetal life strategies are chosen based on a fetal prediction of the postnatal environment in which the individual will eventually live and reproduce. If the fetus makes the right prediction all will be well; if it does not then problems will ensue. Understanding how this happens and why evolution has preserved such a mechanism is an important part of this book. The consequences for our species are particularly dramatic because perhaps for the first time in our evolutionary history, humans now inhabit an environment in which we have not evolved to live.

Accordingly, we hope the book will appeal to a diverse set of readers – both lay people and scientists, those interested in disease and disease prevention, in

pregnancy and, specifically, in a healthy start to life,[3] or in broader evolutionary biology. Inevitably, when a book is written for a range of readers, for some the technical detail in one area will be too much and for others, insufficient. We have tried to write the book so that it can be read in its entirety, or as individual chapters. We have also tried to give a brief explanation of technical terms, but also to structure the book so that more technical sections can be skipped. We hope that the totality of the book is stimulating and thought-provoking to the reader.

This book and our ideas build on the enormous contributions of scientists throughout the world, many of whom are our friends and colleagues, and we are grateful for the many interactions we have had with them. Our own experimental work is based on the contributions of numerous colleagues, fellows and students and we each are privileged to work with truly intellectually exciting and scientifically rigorous groups. All have helped build towards the ideas we have synthesised in this book. We acknowledge, in particular, the following. In Auckland: Frank Bloomfield, Bernhard Breier, Wayne Cutfield, Jane Harding, Mark Harris, Paul Hofman, Mark Oliver and Mark Vickers. In Southampton: Fred Anthony, Caroline Bertram, Lee Brawley, Felino Cagampang, Iain Cameron, Cyrus Cooper, Caroline Fall, Keith Godfrey, Lucy Green, Hazel Inskip, Shigeru Itoh, Alan Jackson, Catherine Law, Rohan Lewis, Christopher Martyn, Jim Newman, Hidenori Nishina, Clive Osmond, Takashi Ozaki, David Phillips, Kirsten Poore, Malcolm Richardson and Tim Wheeler.

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[3] See D. J. P. Barker, *The Best Start in Life* (London: Century, 2003).

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We are privileged to work at two Universities, Auckland and Southampton, that have allowed us to build significant research enterprises focused on the questions detailed in this book. It is pleasing to see our personal interaction as authors reflected in growing joint research enterprise between our institutions in this field.

Writing a book when the two authors are at opposite points on the globe has meant strong commitments from our families. We chose to write together, and all parts of the book (actually every paragraph) is the product of our joint effort. To our wives, Judy and Clare, and our children, Katie, Josh, Antonia and Jack, we are most grateful for forbearance with our many absences and long nights on the phone (by definition it was always night for one of us!).

PDG
MAH
Auckland, Southampton and places in between
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