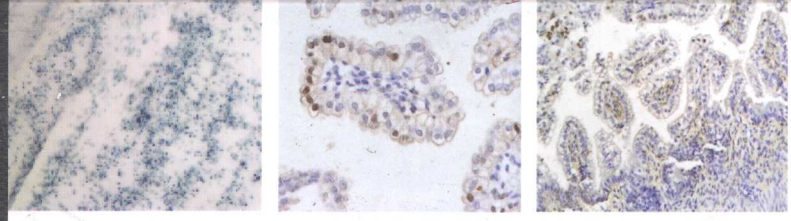

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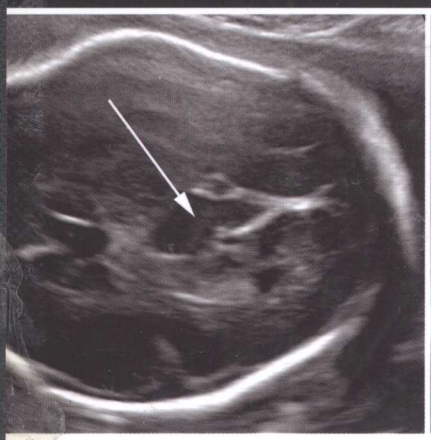
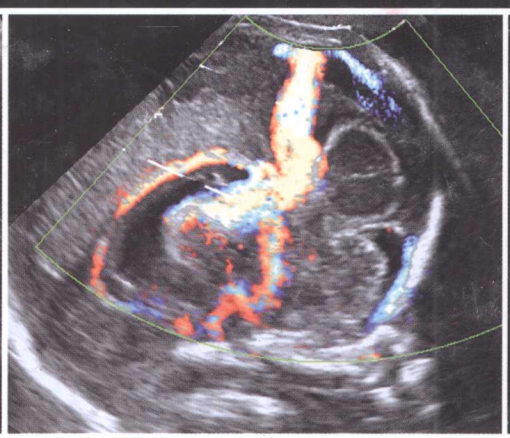
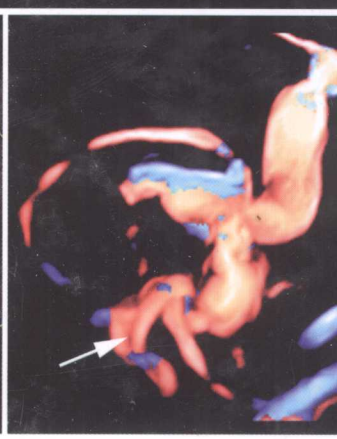
FETAL MEDICINE

Basic Science and Clinical Practice







Foreword by John Queenan

SECOND EDITION

CHURCHILL LIVINGSTONE
ELSEVIER

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FETAL MEDICINE:

Basic Science and Clinical Practice

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Foreword

The last half-century has been an extraordinary time for Fetal Medicine. At the outset, the ravages of prematurity, pre-eclampsia, Rhesus disease, diabetes mellitus, and even rubella took a large toll on perinatal survival. Modalities such as amniocentesis, ultrasonography, and cardiotocography were not yet available to aid the physicians and nurses caring for high-risk pregnancies. Little was known of fetal physiology or the pathophysiology of fetal disease. In the last 50 years, the inner sanctum of the fetus was probed and tested with medicines, needles, scalpels, and imaging. The secrets of the fetus were systematically explored, and new tests and treatments were developed. This exciting era brought major advances in diagnosis, treatment, and prophylaxis for the fetus.

The fetal medicine scene is quite different today. Perinatal mortality and morbidity have decreased remarkably. Through active immunization, rubella has almost disappeared. Through passive immunization, Rhesus disease is markedly decreased. Fetal aneuploidy can effectively be detected by prenatal genetics, even in the first trimester. Diabetic pregnancies, when appropriately managed, lead to outcomes similar to non-diabetics. Preeclampsia is still common, but the management has lowered the morbidity and mortality for both mother and infant. Unexpected iatrogenic prematurity has almost disappeared because of accurate dating of gestations. Neonatal intensive care nursery skills and equipment have made it possible to save babies born at 23–24 weeks of gestation, while 50 years ago survival rates were low before 34–35 weeks. Now, with fetal surveillance, corticosteroids to promote fetal pulmonary maturity, tocolysis to permit administration of such, and transfer to an appropriate facility for delivery, the prospects for the premature infant are greatly improved.

The two editors of this book were central to the many improvements of Fetal Medicine. As perinatal pioneers, they contributed enormously to the development of new knowledge. Professor Rodeck unlocked the secrets of in-utero health and disease with his fetoscopy, developing diagnostic and therapeutic modalities for the fetus. Professor Whittle has made important contributions in genetics, fetal evaluation, and treatment. What better experts could take on the arduous task of creating a definitive second edition of this textbook?

Unlike most books on high-risk pregnancies, which cover the maternal and fetal aspects, this textbook concentrates on the fetus. They present a comprehensive opus that is truly international, selecting qualified authors who can discuss the basic science as well as the clinical aspects of perinatal problems. This is an essential resource with extraordinary information on embryology, physiology and genetics, and clinical management. It will serve all who care for high-risk pregnancies in the future as we try to conquer the remaining problems causing compromised pregnancy outcome, and to make the next half century of Fetal Medicine even more revolutionary than the last.

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Prefaces

Preface to the second edition

The response to the First Edition was extremely positive but when a Second Edition was suggested, we thought long and hard. The many innovations that have occurred since the publication of the First Edition in 1999 made a revision imperative and rather to our surprise we agreed to the enterprise! We have kept to the Principles outlined in the Preface to the First Edition. We were determined to keep the basic science and to combine it with practical guidance in a variety of clinical circumstances. But there have been many changes. Some chapters are new and others have been completely updated. A self-assessment section with clinical scenarios has been added. We hope that this and the retention of the Appendix with charts of fetal measurements will both assist trainees with learning and continue to add to the value of the book in daily practice. Most sections have been pruned and this Edition is leaner, slimmer, and we believe, fitter.

We have been fortunate that such a constellation of international experts has so generously given their time to share their expertise and we are deeply indebted to them. They have delivered the most up-to-date information possible and balanced the flavour of local practice and experience with a global view. This is a strength which provides individual clinicians, faced with a particular problem, a broader perspective to guide management.

We are also most grateful to our publisher and in particular to Ailsa Laing and Kerrie-Anne Jarvis for their unfailing and patient support and to the commissioning editors, initially Ellen Green and subsequently Pauline Graham. We would also like to thank John Queenan for his constructive comments and kind words.

CHARLES H. RODECK
MARTIN J. WHITTLE

Preface to the first edition

The demise of the large textbook has been repeatedly announced, yet it has failed to happen – why? Perhaps because they provide a summation of knowledge and define a discipline. We believe that this book, the first devoted to Fetal Medicine, fulfils these functions. We thought it essential to include the relevant basic science because the rate of increase in information is outstripping the ability of clinicians to keep up. New scientific terminology and language pose barriers to understanding which we hope that this book will help to overcome.

In such a multidisciplinary field it has been impossible to be all-inclusive: we have preferred to be selective, including only core subjects. In embryology, topics were chosen to illustrate scientific principles, and in neonatology, for their immediate relevance to the fetus. After some initial reluctance, maternal medicine was excluded. Although currently most feto-maternal subspecialists work in both fields, it is likely that a separation will occur in the near future and there are numerous excellent texts dealing with maternal medicine.

We make no apology for some overlap and repetition in a number of the chapters. This has given authors the freedom to express differing views and to develop their own themes, thus maintaining the internal consistency of their chapters. Neither do we apologise for not imposing either cis- or trans-atlantic spelling. That would seem parochial in comparison to the theme of the book and its global authorship and readership.

The development of this book has taken over 10 years, partly due to a series of upheavals in the publishing world. Much credit for its conception must go to the persuasive and persistent charm of Sylvia Hull. Others who have helped to nurture it include Lucy Gardner, Antonia Seymour, Prudence Daniels, Deborah Russell, and most recently Miranda Bromage and Rachel Robson, and they deserve our gratitude. Most of all, we thank our contributors. Their time (much of it doubtless after midnight), expertise and perseverence have provided us with superb chapters.

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Contents

SECTION 1

Early fetal development

CHAPTER 1

Early concepts and terminology

Patricia Collins

KEY POINTS

- A revision of the 19th century terminology still used to describe early embryos, particularly the outdated term 'germ layers'
- Review of the terms now used for specific embryonic cell populations and the usefulness of histological terms
- Reviews the axes of the early embryo and the terminology used to describe animal and human bodies

Traditional accounts of embryology rely on familiarity with the germ layer concept developed in the latter years of the 19th century. All students are acquainted with ectoderm, endoderm and mesoderm layers and accept the grouping of mature tissues and systems with these layers. However, it is apposite, in the early years of the 21st century, to review and question the usage of our old terminology, and the assumptions which have developed as a consequence, and move forward stating our present knowledge base using the most appropriate language with which to express our existing concepts and hypotheses.

The transitory nature of our conceptual frameworks is acknowledged. We know that the 'snapshots' of knowledge in textbooks may be outdated by the time of publication and are now more likely to turn to the Internet to find the latest publications on a topic. However, the language we use to describe even the most recent findings is still rooted in the past and in many ways hinders our ability to explain developmental processes.

The rapid advances in developmental biology which have increased our understanding of embryological processes have elucidated many cell lines, each of which gives rise to parts of the embryo, each cell type being important in different stages of development. The relatively new methods of cell study, e.g. inter alia, cloning cells taken from early and later stages of development, and production of chimeric embryos where cells from, for example, quail embryos are substituted for cells in chick embryos, have compounded the problem of how to describe cell populations in early embryos so as to marry the older embryological terminology everyone is familiar with to the newer, more specialized, vocabulary of developmental biology.

It has been suggested that to cope with the complex and often conflicting terminologies in embryology, nomenclature relating to the histological appearance of cells is more helpful than the older traditional concepts[1–3]. Indeed, the advances in embryology now make it increasingly difficult to relate older and newer language. This first chapter will give a brief account of the way the older terminology developed and move on to explain the usage of the more recent terminologies.

THE ORIGIN OF THE TRADITIONAL LANGUAGE OF EMBRYOLOGY

The traditional language of embryology comes from work and concepts generated between 1830 and 1900 when, in the mid-1800s, the theory of evolution was being formulated. Ernst Haeckel[4], particularly, promoted a concept which stated that embryos would pass through all the previous evolutionary stages, resembling a series of extant or extinct adult animals as they recapitulated evolution during development. Thus, Haeckel designated a *blastula* stage of development, where a sphere or bilaminar layer of embryonic cells was present, and a later *gastrula* stage achieved after the blastula cells had invaginated to produce more than one or two layers. It is from Haeckel we have the term *gastrulation* to describe the process where cells initially on the embryonic surface move inside the embryo to produce intraembryonic cell populations.

At this time, the instruments for examining embryos were rudimentary and the cell theory was still relatively young. Scientists of the day saw layers of tissue rather than the individual cells composing the layers. Even in those studies where it is clear from the publications that cells could be seen, distinctions between early embryonic cell types probably could not be made with the instruments available. The concepts thus generated by these early embryologists were products of their time, dependent on the methods of experiment and observation customary when they were formulated.

During the process of gastrulation, cells from the outside of the embryo move to the interior and become organized in specific sites. The concept of three main or *germ layers* was

formulated by Von Baer[5] and promoted by the Hertwig brothers[6] who supported the doctrine that three germ layers were found in all animal embryos. The layers of adult two-layered creatures had been named *ectoderm* and *endoderm* by Allman[7] and, later, the term *mesoderm* was introduced to describe both the structure that intervened between the ectoderm (exoderm) and endoderm (entoderm) of triploblastic animals and the corresponding embryonic middle layer[4]. At the same time, the more specific embryological terms *epiblast*, *mesoblast* and *hypoblast* were used by Balfour[8] in his studies on chick embryos. Thus, for most of the 20th century, textbooks supported the notion that the tissues of the developed body were derived from one of the three germ layers. While this is not untrue in simplistic terms, the accent on three layers has obfuscated the dynamic differentiation processes occurring in embryos and hindered much description of what can be seen histologically.

A similar process occurred with the description of external embryonic form. Von Baer noted that all vertebrate embryos pass through externally similar stages and Haeckel published a series of drawings demonstrating remarkable similarity between embryos which go on to become very dissimilar adults. This latter concept remained unchallenged for over a century. Recent examination of Haeckel's pictures, together with a clear analysis of the developmental stages of various organs in each embryo revealed a story much closer to the Emperor's new clothes. Richardson[9] noted that drawings by contemporaries of Haeckel show much more accurate interpretations of mammalian embryos of the same developmental stage with clear differences between them. He noted that Haeckel's drawings had given a misleading view of embryonic development. Thus, the idea of one stage of development where all vertebrates are the same, promoted extensively at the turn of the 20th century and repeated unchallenged, obfuscated what really occurs in a number of vertebrate embryos and hindered the search for what is actually present in embryos by limiting our language and expectations.

A description of the developmentally based terminology which recent textbooks of embryology embrace follows, outlining the initial derivation and fate of the early cell lines. As can be seen, the complexities of development now require a redefining of the older terminologies and the introduction of new ones to describe the changes taking place and the cell types involved.

RECENT NOMENCLATURE OF EARLY DEVELOPMENT AND SPECIFICATION OF CELL ORIGIN

The initial zygote cleaves into a number of cells which, because of their position and experiences, have different fates. The earliest positions of cells in the morula will influence the first decision between trophoblastic cells, which will give rise to the placenta and membranes, or embryonic cells. The initial embryonic cells, which are arranged as a disk, are collectively termed *epiblast*. These cells will produce all of the embryonic cell lines and some extraembryonic cell lines. The epiblast cells are supported by an underlying *hypoblast* layer of extraembryonic cells which will later become sequestered into the yolk sac wall. An interaction between epiblast and hypoblast gives rise to the *primitive streak*, a region of cell proliferation and movement, that defines the craniocaudal axis of the embryo. Passage through

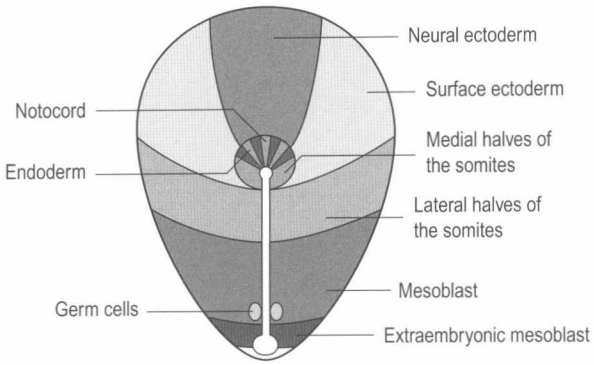

Fig. 1.1 Predictive fates of the epiblast cell population at the time the primitive streak is present. (From *Gray's Anatomy*, 39th edn. Edinburgh: Churchill Livingstone, 2005.)

the primitive streak will confer a fate onto cells specified by the position of invagination or the time of invagination[10]. Predictive fate maps of the epiblast have been constructed from data on the differentiative fate of cells taken from different regions of the embryonic disc and cloned (Fig. 1.1).

The primitive streak extends from near the center of the embryonic disk, where it forms the *primitive node*, a curved ridge of cells, to the edge of the disk close to the early connection of the embryo to the developing placenta. Passage of proliferating cells through the primitive node gives rise to the axial cell populations, the *notochord* and the *medial halves of the somites*, and also to the *endoderm* which spreads out beneath the epiblast displacing the hypoblast laterally into the yolk sac wall. Passage through the rostral portion of the primitive streak, however, produces the *lateral halves of the somites* and the middle portion of the streak produces the *lateral plate cells*[11,12]. The next caudal portion of the primitive streak gives rise to the *primordial germ cells*. These are sequestered in the extraembryonic tissues very early on in development and do not return to the embryo until the early gonads have formed. The most caudal portion of the streak contributes cells to the *extraembryonic tissue*.

Once these cells have passed through the primitive streak, the remaining epiblast contains cells populations which will become the surface epithelium of the embryo (this still retains the term 'ectoderm') and the neuroepithelium of the embryo which will form the central, peripheral and autonomic nervous systems. This population is termed 'neurectoderm' prior to neurulation; it is found in front of the primitive node.

The cells within the epiblast are epithelial, when they pass through the primitive streak they undergo a change in morphology allowing them to migrate. This new migratory population is initially termed *mesoblast*[3,13]. All of the early migratory cells derived from ingression through the primitive streak revert to epithelia when they arrive at their final destinations and subsequently form proliferative centers. Cells produced from these early germinal epithelia form populations described as *mesenchyme*, further subdivided according to their position in the embryo. Special populations of mesenchyme also develop from the neural epithelium. At the margins of the neural plate are clusters of neuroepithelial cells termed *neural crest cells*. These cells will form the peripheral nervous system in the trunk and head and an extensive mesenchymal population in the head, often termed 'ectomesenchyme'. The neural crest is