Perspectives in Physiology
Published on behalf of The American Physiological Society by Springer

Lawrence D. Longo

The Rise of Fetal and Neonatal Physiology

Basic Science to Clinical Care

Second Edition

Springer

Perspectives in Physiology

Published on behalf of The American Physiological Society
by Springer

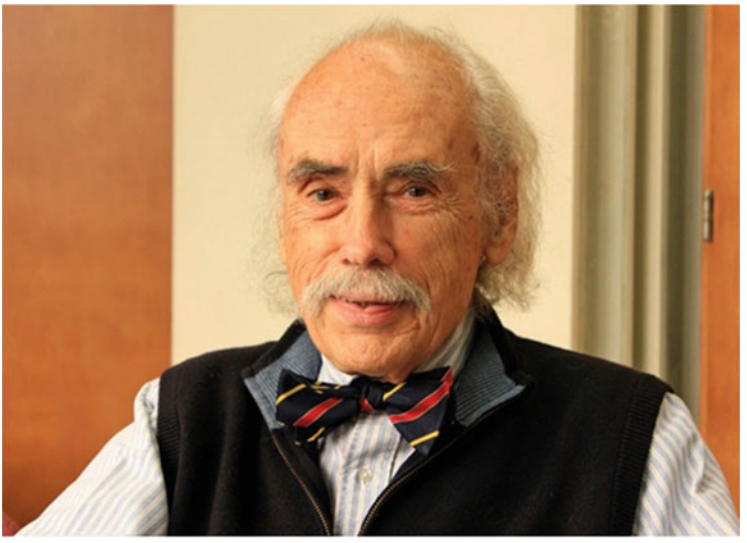
Perspectives in Physiology

This fascinating series seeks to place biomedical science inside a greater historical framework, describing the main pathways of development and highlighting the contributions of prominent investigators.

This book series is published on behalf of the American Physiological Society (APS) by Springer. Access to APS books published with Springer is free to APS members.

More information about this series at http://www.springer.com/series/11779

APS publishes three book series in partnership with Springer: Physiology in Health and Disease (formerly *Clinical Physiology*), *Methods in Physiology*, and *Perspectives in Physiology* (formerly *People and Ideas*), as well as general titles.



Lawrence D. Longo (1926-2016)

Lawrence D. Longo
This work was completed by Steven M. Yellon, Ravi Goyal, Ciprian P. Gheorghe, Justo Alonso, and Michael A. Kirby

The Rise of Fetal and Neonatal Physiology

Basic Science to Clinical Care

Second Edition

Foreword by Kent L.R. Thornburg

Springer

aps American Physiological Society

Lawrence D. Longo (deceased)
Formerly at:
Longo Center for Perinatal Biology,
Loma Linda University School of Medicine
Loma Linda, CA, USA

This work was completed by

Steven M. Yellon
Professor of Physiology
Departments of Basic Sciences and Pediatrics
Lawrence D. Longo Center for Perinatal Biology
Loma Linda University, School of Medicine
Loma Linda, CA, USA

Ciprian P. Gheorghe
Assistant Professor of Neonatology
Department of Obstetrics and Gynecology,
Loma Linda University, School of Medicine
Loma Linda, CA, USA

Michael A. Kirby
Professor of Anatomy
Departments of Pathology and Human Anatomy and Pediatrics
Lawrence D. Longo Center for Perinatal Biology
and
Associate Vice-President Research Affairs
Loma Linda University, School of Medicine
Loma Linda, CA, USA

Ravi Goyal
Associate Professor of Physiology
Department of Basic Sciences
Lawrence D. Longo Center for Perinatal Biology
Loma Linda University, School of Medicine
Loma Linda, CA, USA

Justo Alonso
Professor and Chairman Department of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
University of Uruguay, Montevideo School of Medicine
Montevideo, Uruguay

Perspectives in Physiology
ISBN 978-1-4939-7482-5 ISBN 978-1-4939-7483-2 (eBook)
https://doi.org/10.1007/978-1-4939-7483-2

Library of Congress Control Number: 2017955620

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer Science+Business Media, LLC
The registered company address is: 233 Spring Street, New York, NY 10013, U.S.A.

Foreword to the Second Edition

When you ask a successful scientist about their training, he or she will inevitably refer to one or more heroes who have changed the course of their careers. In every case, the hero being revered will have been a brilliant scientist and marvelous mentor. In addition, he or she will have had a gift for writing, caring, nurturing, and teaching academic survival skills. Thus, for those of us who are among the privileged who pursue the secrets of the natural world, we have our heroes to thank. Hero reproduction, it appears, is the mechanism by which cutting-edge science is passed from one generation to the next.

In my case, I was molded by professors who encouraged me, beginning as an undergraduate. Those who influenced me most included Drs. Elver Voth, Howard Hilleman, Job Faber, and James Metcalfe. However, not all of my heroes were overseeing my education. I came to know and appreciate others at national scientific meetings and at different universities during my travels. These included Geoffrey Dawes, Robert Boyd, and David Barker. In addition, there were scientific contemporaries from universities around the world with whom I "grew up" in the field and for whom I have great admiration to this day.

I am particularly pleased to honor one of my heroes in this foreword, the late Lawrence D. Longo (1926–2016). Dr. Longo had the personal appearance, not so far from the Albert Einstein look, and the intense personality of a natural born leader. Not only have I admired him for decades because he paid so much attention to me when I was a junior faculty member, but more because I discovered that he was a source of encouragement to a host of people in the field of human development both on a personal level and as a cheerleader for the Society for Reproductive Investigation.

Over the course of Dr. Longo's long career, he saw dramatic changes in the field he loved most—pregnancy and fetal development. As for all scientists in this highly important field, his lineage began decades ago with greats such as Joseph Barcroft (1872–1947) at Cambridge University, Donald Barron (1905–1993) at Yale University, Geoffrey Dawes (1918–1996) at Oxford University, Geoffrey Thorburn (1930–1996) at Monash University in Melbourne Australia, Elizabeth Ramsey

(1906–1993) at the Carnegie Institution in Washington, and Jeffrey Robinson (professor emeritus) at the University of Adelaide, Australia. It was the powerful contributions to the field of pregnancy and fetal development of these leaders and their colleagues that led Dr. Longo to enshrine a few of them in this volume and by so doing remind young scientists of their roots.

By the mid-twentieth century, the field of fetal development was warming up. The pioneering work of these aforementioned forefathers and mothers set the field aflame and the fire spread across the globe, especially across North America, Australia, and New Zealand. Longo himself was swept up in the quest to understand the mysteries of the invisible, and mostly inaccessible, fetus. Once it was discovered in the 1960s that the sheep fetus could be studied chronically in its natural habitat, it became the model of choice for dozens of groups worldwide. The resulting information rush brought a thorough description of fetal hemodynamics and metabolism, placental blood flow, brain development, endocrine regulation, and pulmonary maturation. We now take for granted our understanding that the hemoglobin of the fetus binds oxygen more tightly than does its mother's, that blood flows through the heart muscle of the fetus at twice the rate found in the adult heart, and that the fetus must drink its amniotic fluid and practice breathing before it is born. From all these marvelous discoveries, modern obstetrical medicine owes a great debt to fetal physiologists who discovered the intricacies of development and which now provide the foundation for the practice of clinical fetal medicine.

New technologies appeared during the 1970s and 1980s that allowed fetal measurements that were not previously thought possible. These included measurement of fetal blood flow with radiolabeled microspheres, miniature Doppler flow sensors, Doppler ultrasound, and electromagnetic and transit time flow sensors in addition to implantable electrodes to measure electrical activity in the brain and striated and smooth muscle. Many discoveries in the fetus, like surfactant therapy from Dr. Mont Liggins' laboratory in Auckland, changed clinical practice for women and their fetuses forever. Toward the end of the 1980s, after hundreds of papers had been written demonstrating the homeostatic mechanisms ensuring fetal survival in the womb, scientists began to wonder what new frontiers would be needed to provide better clinical applications of the knowledge gained over the previous 30 years. Then, without warning, the landscape changed dramatically.

In 1989, Professor David J.P. Barker from the University of Southampton published data showing an inverse relationship between mortality from ischemic heart disease and birthweight among 15,000 men and women in Hertfordshire, UK. Many fetal scientists, including me, were skeptical, lacking an obvious biological explanation. However, Barker was undeterred. He embraced the world of basic science and sought out fetal physiologists to find answers. Soon, a new field of so-called fetal programming, now officially called the developmental origins of health and disease (DOHaD), was born. Suddenly, experts on pregnancy and fetal development were uncovering mechanisms explaining the very core of human existence, the early life origins of chronic disease. To this day, fetal biologists and pregnancy experts sprinkled across the Western world are making headway in

understanding how developmental plasticity in early life leads to vulnerability for disease in adulthood. Until their deaths, Drs. Longo and Barker were among them.

With a sudden link to human disease, no longer would fetal biologists be content to describe obscure facts regarding physiological development. The quest had changed. Now the question for all developmental biologists became: what are the mechanisms though which environmental stressors influence reproduction and postnatal development and lead to vulnerability for adult-onset disease? This change in mind-set came at a time when the prevalences of obesity, diabetes, and uncontrolled hypertension were increasing year after year as they are today. The rapid epidemic of chronic disease in the USA over the past 20 years cannot be explained by changes in DNA sequence. Rather, based on recent evidence from fetal biologists, one can fairly argue that the recent unprecedented increases in chronic diseases are rooted in responses to environmental challenges during early development. Thus, current students of development have a new mandate linked directly to human health.

Dr. Longo was clever of mind; he intuitively understood the importance of the developmental origins of disease as a game changer for the field of fetal physiology. Over his career, he gained expertise on one topic after the next as he followed his interests. His focus moved from pregnancy to placental function to fetal cardiovascular function and finally to fetal brain development. In every case, he and his colleagues made highly significant discoveries.

After becoming the director of the Center for Perinatal Biology (1973–2012), he recruited a strong team of young scientists who carried the field forward with enthusiasm. Dr. Longo and collaborators began to study the adaptations made by the vasculature of the fetal brain under conditions of hypobaric hypoxia when pregnant ewes were housed at 12,000 feet at the White Mountain Research Station in California. Their findings led to concerns about how fetuses deprived of oxygen might suffer later as adults, a field of study for which the Loma Linda team is deservedly held in high esteem to this day.

During his long tenure at Loma Linda University, Dr. Longo became an important leader for the entire field because somehow he was able to "adopt" scientists from around the country as part of the Loma Linda family. An invitation to visit the Loma Linda laboratories meant an invitation to join a new family of investigators. Thus, scientists, invited from around the world, came to Loma Linda to join in the quest for answers to the most difficult problems in human pregnancy and late life diseases of offspring. While the contributions made by Dr. Longo and colleagues will be long remembered through their hundreds of significant contributions to the literature, Dr. Longo himself has contributed much more to science than an impressive list of published papers. He modeled for young men and women how to become a scientist of stature and integrity. It is that very contribution to the lives of others that will continue, like heritable DNA replication, to be passed on from this generation to the next.

What makes a person a highly effective mentor? Reliving Dr. Longo's success may go some way toward giving an answer.

Dr. Longo had vision. Visionary people often have trouble keeping their feet on the ground. They sometimes become hopeless utopians. However, Dr. Larry Longo's vision was practical. He envisioned building a world-class group of fetal investigators and along with his talented colleague, Gordon Power, he saw his vision come to fruition.

Dr. Longo had courage. Young people may not know that a great deal of courage is required to build an organization from scratch. Why, because if talent and resources are not forthcoming, the enterprise fails. Overcoming the risk of failure with courage is key to success. Dr. Longo charged into an area of biology, the developing brain, in which he had not previously worked. His early discoveries were highly complex and difficult to explain. Nevertheless, those novel findings now shed new light on the regulation of the vascular elements in the brain in response to hypoxia and apply to millions of people who were deprived of oxygen before birth.

Dr. Longo had a warm sense of humor. No one who knew him will forget his hearty laugh. One time when I visited Loma Linda, I showed our new function curves from the right and left ventricles of the fetal heart. I remarked that Ray Gilbert, one of Dr. Longo's esteemed colleagues, was indeed the father of the fetal function curve. Larry Longo was tickled by the comment and he asked, if Ray was the father, who was the mother. I said I guessed I was. He could hardly stop laughing. In spite of the fact that he was not above being angry over an inept comment by a grant reviewer, or worse, a grant application rejection, he was always able to cool down and resume his true nature as a kind and gentle person who cared about Loma Linda University, his scientific colleagues, and a host of people across the country who knew him as a friend.

When you read this volume, I suggest that you see it through the eyes of Lawrence Longo who was fascinated by history and who knew more about the historical roots of fetal biology than any other person alive today.

Kent L.R. Thornburg

Center for Developmental Health
Knight Cardiovascular Institute
Portland, OR, USA

Moore Institute for Nutrition and
Wellness, Oregon Health & Science
University, Portland, OR, USA

Foreword to the First Edition

The 1960s and 1970s were wonderful times to be doing research in fetal physiology. To be in Oxford during that period was to be in one of the great centers of research activity. I had the good fortune to be at the right place at the right time. Oxford was our Camelot. Colleagues from around the world spoke enviously of one having a "Been to Oxford" (BtO) degree. Geoffrey S. Dawes (1918–1996), Director of the Nuffield Institute for Medical Research in Oxford, was undoubtedly the father figure (some said godfather figure) of fetal physiology in his day. His contributions were of such significance that his position as a giant in the field was unassailable. He had built upon the foundations laid by Barcroft, Eastman, Barron, and those others who had preceded him to define a new field of investigation.

Why was Oxford so special? Partly, it was the lure of that venerable city, and the Oxford "way" of doing things. Partly, it was the coming together of a remarkable group of outstanding and enthusiastic young physiologists working with some extraordinary senior leaders and visitors. There was a critical mass of colleagues and supportive technical staff, and a buzz around Geoffrey's Nuffield Institute. Time was immaterial, there always was someone working at a new problem or ready to share a new finding. Crucial was the realization that the fetus as not just a little adult, but was a distinct, viable entity, with a separate and often quite different physiology. It was clear that everything that we knew about adult physiology did not necessarily apply to the fetus, and needed to be rediscovered or at least reexamined. Every day seemingly brought another discovery, another surprise. The institute was adjacent to the University of Oxford's John Radcliffe Hospital and its Nuffield Departments of Obstetrics and Gynecology and of Pediatrics. The leaders of those departments were sympathetic towards research, and it was quickly clear that this new science had immediate application to clinical practice in obstetrics and pediatrics. The proximity of the institute to the clinical wards, to enthusiastic young physicians, and our attendance at clinical rounds facilitated this process. We were doing translational research and knowledge exchange before it became fashionable, without even the need to give it a fancy name.

Without question, the simultaneous and coincidental development of an array of new techniques was crucial to the opening of this new field. There was a rapid advance from the study of the sheep fetus in short-term acute experiments, *ex utero,* to extraordinary studies with the in vivo chronically catheterized fetal lamb. In 1969, Geoffrey Thorburn had published with John Bassett the rise in plasma cortisol concentrations that preceded the onset of birth in chronically catheterized fetal sheep, and later had helped establish that procedure in Oxford. I shall always remember that great physiologist and chronicler of the placenta, Emmanuel Ciprian Amoroso, returning to the ARC Institute of Animal Physiology at Babraham, Cambridge, from a trip to Australia. I was a graduate student at that time, and Amo lost no chance to sing the praises of Geoff Thorburn and this remarkable advance. Little did I know that in 4 years I would be working with him and I could not have guessed at the influence that he would have on my own career. But, let us get back to Oxford. Mention also must be made of Derek Wyatt, an outstanding physicist and member of the institute, who was crucial in developing many of the flow probes that would be used in these new "fetal" preparations. The new technique of radioimmunoassay had just been developed to the point that we could measure multiple hormones in very small samples of fetal blood. We had techniques for recording electrical signals from the fetal brain in utero, we could measure blood flows and distribution, and we could ask the "undisturbed fetus" questions of critical clinical importance: "how are you? how are your blood gases? what are your glucose levels?" We could measure fetal responses to perturbations, infusions of hormones and drugs, follow physiologic changes through the birth process and into the newborn period. I remember well the time that we were making the first measurements of the rise in Prostaglandin E2 in the fetal circulation before birth. I proudly showed the print out from the scintillation counter to Geoffrey Dawes. He was unimpressed. I had not explained that as the counts went down, the concentration was going up. But then he asked whether this might have anything to do with the decline in fetal breathing movements that occurs at that time, and suddenly I had his full attention, and a year's worth of suggested experiments!

Our scientific advances were helped by good-natured fellowship and by competition. There was great collegiality and daily debate at morning coffee and afternoon tea held around the round table in the lobby of the institute (see my letter to LDL in Chap. 20). Here Geoffrey Dawes was masterful and a wonderful stimulator of new ideas. There was also great debate at the White Hart Pub at lunch time and after work in the evening. It is strange that today we have to force these interactions with scheduled meetings. But, there was also competition. In the early 1970s there were three related Medical Research Council (MRC) program grants at Oxford, led by Geoffrey Dawes (GSD), Geoffrey Thorburn (the big G) and Alexander Cuthbert Turnbull (later Sir Alexander; 1925–1990), respectively, dealing with parturition and fetal physiologic changes near birth. The competition in research was and is healthy. It helps to drive us forward. It also infuses an

environment with measureable energy that leads to pride and excitement, and eventually to a legacy of accomplishment. It helps create leadership and lifelong friendships and networks. It was an environment that brought Oxford together at international meetings, particularly in exchanges with other major centers that were emerging at that time. Importantly locally amongst these was the excellent group in Cambridge of Robert Comline, Marion Sliver, successors of Sir Joseph Barcroft in the perinatal research field, with the young Peter Nathanielsz and Abigail Fowden (although, as a Cambridge graduate, I was just a little uneasy with the light blue–dark blue conflict). The University of Oxford Nuffield Department of Obstetrics and Gynaecology photographs from 1974 to 1975 are so revealing of the environment at that time. Virtually every one of the junior staff members and trainees in those pictures went on to hold a major chair or a directorship later in their career, but as colleagues they have remained in touch with each other, bonded by the Oxford experience.

The public environment was also "right" for doing fetal research. In the United Kingdom, the MRC was enthusiastically supportive through staff appointments and research grants; in the USA, fetal physiology was gaining momentum at the National Institutes of Health. The media, the general public, and some key politicians wanted to know about life and development in the womb. Preterm birth occurred in one in ten pregnancies. At a time when we were just starting to learn about the regulation of lung surfactant, the public wanted to know how to prevent preterm birth and how to look after the premature baby. The landmark study of "Mont" Liggins and Ross Howie on the use of glucocorticoids to prevent respiratory distress syndrome was published in 1971. It resulted directly from studies of cortisol infusion into fetal sheep, the perceptive insight of Mont Liggins, and minimal bureaucracy in moving basic research into a clinical trial. Mothers wanted to know how the environment might affect their baby. Research offered answers. The magic and mystique of the environment inside the womb became mainstream reading. A black box was opening quickly with new information based on excellent science. Politicians and funding agencies listened carefully and were extremely supportive.

But research happens in cycles. Often these last only 5–10 years. An area becomes topical, a new approach offers a major advance and folk jump onto the bandwagon, until the research becomes routine. For a short time, grant funding committees and study sections look favorably on something that is cutting edge. It may be a new field of research (such as fetal physiology) a new topic (prostaglandins, insulin-like growth factors), a fascinating and important discovery (surfactant), or the emergence of a new technique (the chronic fetal sheep preparation and assay of hormone receptors). Fetal physiology seemed to happen in a way and at a time that allowed a convergence of these different factors and approaches. The field opened up technically, the translation (such as in fetal

monitoring, stimulation of lung surfactant, or surfactant therapy), was obvious in obstetric and neonatal practice, and that fuelled public interest and media support. Because there was a whole field of fetal physiology to be discovered, the wave lasted a bit longer than many. In many ways this was good. But I also believe that fetal physiologists lost the game or only recognized it when it was too late for them, to the developmental biologists, initially, and then to mice. We missed the fiscal reality of switching from sheep to mice and we were slow to appreciate the power of mutating a gene and the ability to knock in and knockout genes. Of course, we soon became useful in helping to interpret phenotypes (and there was some very naïve phenotypic interpretation of some early mouse knockouts), but the agenda had changed, and a new generation of investigator was driving it.

The field of fetal physiology continues today, of course; that is the nature of scientific waves. But, I think this is what Geoffrey Dawes meant by his oft (mis) quoted comment about the major questions in fetal physiology being answered by the time of his retirement. Most major questions had been addressed at a physiologic level, and needed new genetic approaches to achieve further mechanistic advance. Geoffrey also saw the emerging importance of understanding the fetal origins of adult disease, and championed the meeting in Italy in 1989 where David J.P. Barker presented his very early information to a group of fetal physiologists. If there was an obvious way forward for fetal physiology, it was through understanding the developmental origins of disease. This needed a physiologic approach but had to be coupled with application of different 'omic techniques and epigenetics. But, many Ob-Gyn departments had missed an opportunity to emerge as the hotbeds of university and hospital research, as departments of developmental reproductive biology, combining integrative physiology with cellular and molecular mechanisms of development.

Interestingly, the antivivisection movement was also a factor in the decline of fetal physiology as we knew it. It easily generated more adverse press against research with sheep and subhuman primates, than it did against research on mice. New rules for the conduct of research, new animal requirements, and spiraling costs have driven many classic fetal physiologists out of the animal house. Ironically, the antivivisection movement and fiscal reality actually forced some sheep fetal physiologists toward developmental biology, to develop new models and gain familiarity with new molecular approaches. The new models of translational research that link basic science to population biology and the health care systems will allow fetal physiologists to flourish, and I am optimistic that we are still training a cadre of needed and worthy successors.

Geoffrey Dawes became Director of the Nuffield Institute at age 30 in 1948; 5 years before Watson and Crick published the structure of DNA. At the time, he had only eight publications to his name. This volume portrays him accurately. He was an astute and critical investigator, maintaining the highest standards of scholarship and expecting others to reach those same values. He was sometimes

antagonistic. He was harshly critical when he felt it justified, and he could be polarizing. But if one matched his standard, worked hard and thoughtfully, one gained his respect. You had won a friend, not just in science but for life. But if you had come up through one of the other "schools," it would always be that much harder, and to my mind Geoffrey never accepted you in quite the same way. Over the years he developed a special affinity with Canada, and it has saddened me that our great Canadian Universities did not recognize Geoffrey appropriately for that.

There was also a very compassionate side to Geoffrey Dawes that often went unrecognized. I saw him go to extraordinary lengths to help a colleague with a medical problem, or to assist a student in financial difficulty. He was kind and thoughtful towards the institute staff, knew their names, and quietly would offer his advice or assistance if he thought that it would be helpful. His trainees became his extended family. He followed their progress with great interest and enthusiasm. He shared in the excitement of their discoveries and would enjoy the intellectual discourse with them, clearly proud as they established their independence and faculty appointments. He was, of course devoted to his wife, Margaret. In this book Christopher Redman describes Geoffrey coming into his office, discussing a new finding, and leaving with the comment, "Isn't this fun." That vignette captures the essential Geoffrey Dawes, enthused about good science, just like a small boy.

Finally, I must say a brief word about the author of this book, Lawrence D. Longo. Larry is one of my heroes. He was there, seemingly at the beginning and is still going strong! This volume chronicles the foundations built by the great historic leaders, it tells how they laid the building blocks, and with Dawes and others created a new field of investigation. It tells of the science and of the scientific societies that underpin the discipline. Geoffrey was not there at the beginning of the Society for Gynecologic Investigation in 1953, but he was clearly aware of the advances being made by colleagues across the Atlantic. This volume is a scholarly account of the development of the new field of fetal physiology and the translation of its research to help mothers and babies. It is also a story of relationships, sometimes fuelled by competitiveness, often fuelled by collegiality. It is a story with many subtexts driven by the desire to acquire new knowledge. There was healthy competition, between Cambridge, Oxford, San Francisco, New Haven, Boston, and others as they emerged as leaders and were then linked by new partnerships and the next generation of scientists. There may be other descriptions of the growth of this field, but it is unlikely that there will be any that captures the spirit, the excitement, and the hope for mothers and their children as effectively as Longo has given here. In this volume he has ensured his place as the great chronicler of a generation of investigators, and of a new approach to science. We are fortunate to have a colleague of his intellect and modesty, of such insight into the accomplishment of others. This is the story about how a field of research unfolds. But any new

field needs its champion. For many, Geoffrey S. Dawes was that champion; a man of formidable intellect, a great experimentalist, commanding yet compassionate, the leader of his time.

John R.G. Challis

Department of Physiology
University of Toronto, Ontario, BC
Canada

Department of Obstetrics and
Gynecology, University of Toronto
Ontario, BC, Canada

Simon Fraser University
Burnaby, BC, Canada

University of British Columbia
Vancouver, BC, Canada

University of Western Australia
Crawley, WA, Australia

Preface to the Second Edition

Dr. Longo had sent copies of the first edition of his book on the history of fetal physiology to friends, former postdoctoral fellows, and colleagues around the world. From my conversation with Jimin Suh, the Center's Program Manager who worked closely with Dr. Longo on the first edition, many who read his book, based upon their expertise and insights from research activities, sent thank you notes with praise and comments. Some sent personal recollections of a notable historical figure featured in the book. In addition to comments, other perspectives were provided and wishes that expressed more information would have complemented certain topics. The accumulation of feedback from respected sources and the recognition that important advances in the field had been made since the first edition was published, based upon his proclivity for nocturnal readings, motivated Dr. Longo to make plans for a 2nd edition. Esteemed colleagues with unique expertise were invited to make contributions to this volume with a goal of providing an even more "comprehensive" review of the history and future of the fields of fetal and neonatal physiology. This project added to his many other responsibilities, foremost as principal investigator for an NIH Program Project grant for over 20 years, and an R01 that was approaching 45 years of continuous funding. Though shy of attention, he personally knew almost all of the pioneering modern contributors to development of this field of study during the last half of the twentieth century. His personal contributions were the writing of more than 350 papers, actually with a mechanical pencil; most were peer reviewed, with dozens of chapters and over 20 books. The impact of his efforts on society was enhanced by his writing several United States Surgeon Generals' Reports to Congress (1979–1981) about the Health Effects of Smoking on Pregnancy and Infants, his membership on many NIH Center for Scientific Research grant review panels, and international recognition for publications on the history of medicine. His illustrious career came as a true Clinician scientist based upon a balance of responsibilities for patient care, call schedules, surgery as a practicing Obstetrician, many academic responsibilities with scientific societies, and multiple research grants to support laboratory operations and trainees, often at the sacrifice of

personal time with family. Despite his seniority, he worked at a seemingly indefatigable pace to build a world-class perinatal research center in the School of Medicine at Loma Linda University, as well as helped to create other centers of research excellence as part of promoted infrastructure improvements that are regarded by peer reviewers as outstanding. Amidst all these efforts, no one knew that his work to revise this book would be the last major project of his career. Even when hospitalized in intensive care, revisions were provided and sections of text edited. His efforts are well represented by Lord Byron (1788–1824) in the quote from *Childe Harold's Pilgrimage, Canto 4 [5 issues, page*. 71] (1818), "But I have lived, and not lived in vain. My mind may lose its force, my blood its fire and my frame perish even in conquering pain, but there is that within me which shall tire torture and time, and breathe when I expire." These words and the desire to honor Dr. Longo inspired several past trainees to help complete his final opus. Contributors to this volume were, for Chaps. 12 and 15, Dr. Ravi Goyal, M.D., Ph.D. (Associate Professor, Basic Sciences, LLUSM; postdoctoral fellow with Dr. Longo 2007–2009 and successor principal investigator of several projects); for Chap. 14, Professor Justo Alonso, M.D. (Professor and Chairman, Department of Obstetrics and Gynecology, University of Uruguay (Montevideo) School of Medicine, Fogarty fellow with Dr. Longo 1988); and for Chaps. 11 and 12, Ciprian Gheorghe, M.D., Ph.D. (doctoral student with Dr. Longo 2000–2006). Dr. Michael A. Kirby, Ph.D. (member of the Center since 1986 and Professor of Human Anatomy and Pediatrics, LLUSM) contributed, as Editor, an inestimable time to proof- and fact-check the entire document. My contribution to this book was to serve as Senior Editor, tasked to oversee interactions with the publisher (Spinger) and the American Physiological Society, to maintain a uniformity of voice in writing style, as well as organize and complete unfinished chapters to as close as possible to Dr. Longo's standards. This impossible task was made easier by what seemed like near daily interactions with him from my first day at Loma Linda University, May 1, 1985, for my first and only academic job. This opportunity was, in a large part, due to his efforts. Over many years, our common interests in science and life, intense professional collaborations in research projects and grants, as well as a personal friendship stood the test of time. I am especially grateful for the help of Jimin Suh upon whom Dr. Longo relied during his work to prepare this revised edition. I also wish to acknowledge the exceptional competencies of Charlotte Marshall, who stepped into this role as Editor's assistant to locate sources and references and follow through with due diligence for preparation of this manuscript.

Accordingly, this revision and expansion is dedicated to the memory of Lawrence D. Longo, M.D. (1926–2016). Collectively, our efforts honor his memory as an inspirational and exemplary leader (Director of the Center for Perinatal Biology 1972–2012), mentor, inquisitive polymath, and at times quixotic motivator to push boundaries of understanding. His efforts provided a sustaining contribution to the development of each of our professional perspectives and those of many more trainees and colleagues to pursue important clinically relevant questions. His values, sense of wonder, persistent questions, and thoughtfulness, which encouraged critical thinking and problem solving in a supportive environment, were to the

professional and personal benefit of all who knew him and for a greater good. For Dr. Longo his lifelong quest, included in the Epilogue to the first edition of this book (p. 487), could be summarized as to advance in practical and theoretical ways the understanding of fetal and neonatal physiology so as to lessen the gap between fundamental and clinical sciences and reduce perinatal morbidity and mortality. He appreciated that a vast *terra incognito* of unknowingness remains, as evidenced by the recalcitrance of current preterm birth rates and the epigenetics of fetal origins of adult diseases. Clearly, the task of basic and clinician scientists is to stand on the shoulders of pioneers in this field, brought to current attention by this treatise, to generate replicable data that promotes useful knowledge of the mechanism through which species reproduce with successful pregnancy and the natural process of birth. The critical value of this understanding must be widely communicated as having enormous benefit to confront challenges to the health and well-being of present and future generations, as well as surmount the impact of hypercompetition for dwindling resources that creates risk for academic life as we know it. As Dr. Longo so often said, "Our task therefore is clear: it is to Persevere!"

August 2017 Steven M. Yellon

Preface to the First Edition

> History is always best written generations after the event, when cloud, fact and memory have all fused into what can be accepted as truth, whether it be so or not" (Theodore Harold White 1961, p. 188)

It was in the autumn of 2008 that Charles Evans Wood, of the University of Florida, Gainesville, chairman of the program committee of the Fetal and Neonatal Physiological Society, invited me to present the Geoffrey S. Dawes Memorial Lecture at the 2009 meeting of that society. This lecture, initiated in 1998 to honor Geoffrey Sharman Dawes (1918–1996), traditionally has been presented by an established investigator who reviews some aspect of his or her studies during the previous several decades. Rather than follow that formula, however, I developed a different plan. As one interested in the history of ideas and the evolution of medicine, for some time I had thought that it would be of value to document some of the major issues and events associated with the genesis and development of the rather specialized field of fetal and neonatal physiology. This was, in part, because of its relatively brief history of less than a century, but also because of its enormous contributions to understanding functional physiologic principles, and because of its concentration on a vital and yet often overlooked aspect of biomedical science that has made a profound impact on clinical medicine.

Among the seminal figures and major forces in developing the field of fetal and neonatal physiology was Geoffrey S. Dawes of the Nuffield Institute for Medical Research, University of Oxford. Trained as a physician, he dedicated his career to understanding the physiologic and pharmacologic basis of important clinical problems relating to the developing organism. In a sense, this monograph could be viewed as a case study of the role of an individual scientist, and many of the individuals he trained, in fostering, advancing, and shaping a given field of research. Dawes' scientific career covered a period of 55 years (1941–1996), during which time he published over 220 papers. Included among these were a number of highly cited scientific contributions, major reviews, introductions to symposia, and chapters in books. As noted in the Foreword by John Richard George Challis,

critically, Oxford's Nuffield Institute served as a seedbed and salutary environment for the education and training of a generation of bright young scientists.

Several individuals have asked why I would undertake such a formidable endeavor. Actually, about a decade ago I had commenced working on an article reviewing some of Geoffrey Dawes' many contributions to life. We had been good friends, meeting once or twice a year in Oxford, at international meetings, or my home base in Loma Linda, and I had high regard for his work. Within several years the project had expanded beyond a mere review. Then, following the 2009 Dawes Lecture I realized that to place it all into perspective the enterprise would require at least a small monograph. Several other reasons are relevant.

I probably am one of the last people alive who knew most of the leading figures (with the exception of Huggett and Sir Joseph Barcroft) and lesser lights who contributed to the evolution of ideas, methodologies, and the synthesis of the problems and issues of developmental physiology. In addition, I have participated with many of these notables in relatively small seminars, large conferences, National Institutes of Health (NIH)-supported study sections, and various brainstorming sessions to identify some of the vital issues and challenges that lie ahead.

Also over the years, I have conducted active correspondence with these individuals on a regular basis, and have had the pleasure of having a large number serve as visiting scientists and seminar speakers at our Center for Perinatal Biology. Almost without exception, these discussions have been an enriching experience. Remembrance of many of their comments, experiences, frustrations, and insights, can perhaps provide a thoughtful background for the vicissitudes in science, and the life of the mind.

In addition, I elected to survey this field in an effort to assist young investigators, both basic scientists in physiology as well as clinical researchers in perinatology—fetal and neonatal clinical medicine—to gain an appreciation of their heritage and what has gone before. With today's World Wide Web, information technology, and nanosecond communication, it is sobering to acknowledge that for many young investigators, that which is more than a few years old is *terra incognito*. In general, we live in an ahistorical age. Life is for Now—the Present. For most of the biomedical literature, reference citations in MEDLINE and PubMed go back only to the late 1940s. Thus for practical purposes, contributions before that time simply do not exist. Our perpetual, annihilating present tends to sever our kinship with the past. A sense of our history and tradition, however, argues for the continuity of thought, experience, and feeling that accompanies the journey across the gulf of time. Without our hieroglyphic scribbling, we lose not only the heritage of the past but also our perspective and outlook, and our sense of who and where we are. With the arrangement as presented, readers will have the ability to review quickly the background of a given problem in a single chapter or subchapter. In addition to the story itself, perhaps of greatest value will be the accompanying references (each of which I have perused myself, many in great detail), which they may read and evaluate for themselves. In the present essay, I have attempted to present some of the epistemology of the threads of scientific thought in the context of their times. Nonetheless, we cannot ignore the words of Theodore Harold White (1915–1986)

that opened this Preface, and found in his *Making of the President* (White 1961). As the Harvard pediatrician Clement Andrew Smith (1901–1988) observed regarding this aspect of developmental physiology, growth in knowledge increases desire to understand its special fields, and "this is particularly true of those periods during which life is more dynamic. In no other brief span of existence can such profound alterations and adjustments be studied . . ." (Smith 1945, p. 3).

Nonetheless, several caveats are in order. Although I have attempted to be reasonably complete in considering the experimental studies of various investigators, rather than exhaustive detail, my goal has been to stress the significance of their contributions. Because of the many subjects encompassed by this field of research, and its complexity and progress, the present essay makes no attempt to survey the topic either *in extenso* or to the present day. Rather, it focuses on the role of some individual scientists and those in their circle. Also because of the extent and vastness to which this field has expanded, I have limited the review chiefly to the second half of the twentieth century, considering issues that came to the fore during that time. One might ask, where does history end, and contemporary physiology commence. As can be appreciated, no history of a given field of discipline can be completely current and up-to-date. With each new day and passing week and month, the advances move the frontiers and expand the horizons. With that in mind, for the most part the present survey concludes about the time of Geoffrey Dawes' death in the mid-1990s.

As a corollary, so that this synthesis may be of value to investigators and others with interest in this facet of science, the general bibliography is rather extensive, and that for Dawes includes every paper of which I am aware he wrote (abstracts are not included). The bibliography also includes a number of review articles and volumes that the interested reader may consult to pursue a given topic in depth. Although the over 2,000 references given may appear somewhat exhaustive, it constitutes only a tithe of those papers published in the field during the period of this survey. As such, I trust that these may be of value as a "taking-off" point for one who wishes to explore the topic in greater depth. Importantly, rather than being viewed as an encyclopedic list of names, dates, and isolated facts, I trust that these would help to place the rise of fetal and neonatal physiology in its proper context. In the paragraph that contains the opening quotation of Theodore H. White, he notes, "What can be reconstructed now out of the contemporary recall of those present must be seen as a fog-shrouded range of facts in which occasionally one peak or another appears at a given hour of the day, but whose connection to the next peak of facts is obscured by the clouds in between" (White 1961, p. 188). Or as Napoleon Bonaparte (1769–1821) is alleged to have stated, "What then is ... the truth of history? A fable agreed upon." A work in progress, history is best served by constant reanalysis and rewriting, as opposed to a museum-quality sculpture in resplendent marble.

An additional caveat is in order. For the most part, investigators in this field worked in what Thomas Samuel Kuhn (1922–1996) referred to as canonical "normal science," or "current paradigm." That is, their studies were conducted within a relatively restricted "model" or "system" with an accepted body of

concepts, techniques, and methodologies that guided their thinking and worked to determine the problems to be explored (Kuhn 1962). Several discoveries of what might be regarded as "revolutionary science" or "paradigm shifts" occurred during this period, such as that of the role of the fetal hypothalamic-pituitary-adrenal axis in the initiation of labor, and the role of pulmonary surfactant in respiration. However, despite a number of breakthrough advances, these were not typical of the period as a whole.

That being said, a number of exclusions and gaps will be evident to the reader versed in this discipline. From the standpoint of contemporary biomedical science, for the most part, much of what is reviewed is general organ physiology, with little consideration of advances in cellular and molecular biology. In fact, some would regard this era as "nineteenth-century" descriptive science, phenomenology, or worse. Nonetheless, it is important to recall that our present understanding is based on previous description of fundamental facts and advances. In the words of Sir Isaac Newton (1642–1727) and those before, "If I have been able to see farther than others, it was because I stood on the shoulders of giants" (Merton 1965).

As is well known, "Clio's many mansions" of history may be considered from a number of standpoints: macro-, micro-, global, national, regional, local, social, cultural, political, economic, biographical, and others. For the most part, the present essay is a combination of technological science and internal history. It also includes a fair bit of biography. I would like to think that not inappropriate, for as Ralph Waldo Emerson, (1803–1881) observed, "All history becomes subjective . . . there is properly no History, only Biography" (Emerson 1883, p. 5). As one who has spent almost five decades as a laborer in this field, as noted an advantage in this approach is that with the exception of the very earliest workers, I knew each of the contributors and many were dear friends. Thus, without sounding self-serving, I would like to think that I have more than superficial insight into the developments and issues involved. A limitation, of course, is that in this presentation only a cursory attempt is made to include a number of related social, cultural, political, and economic aspects. In part, the constraints of scholarly research, but also the limitations in publication, require focus of narrative. Although considering chiefly internal events and the "foreground," I have attempted to place the work within the context of its times. In this regard, I deliberately reject the concept of "continuity" in the development of this field of research. Also, the present essay makes no attempt to resolve certain battles of priority of particular innovation, or to impose "progressive" or teleological schemes on this record. A "Whig" view of historical progressivism (Butterfield 1965), this is not.

In preparing this work it has been inspiring to recall the fine, dedicated individuals and the accomplishments of those who have labored so diligently to develop this field of research—to glimpse the greatness of some of the early achievements that we now take for granted. Rather than being the definitive history, however, I trust that it will be viewed as one perspective of fetal and neonatal physiology, albeit one that is rather personal.

In closing, I am particularly grateful to a number of colleagues, many of whom worked at Oxford's Nuffield Institute, who shared stories, anecdotes, and

impressions of their work and interactions with other colleagues. Importantly, I am in great debt to Jimin Suh who worked indefatigably in helping to locate obscure references and other sources, and to prepare this manuscript in its present form. She is absolutely the finest associate for whom one could wish.

Loma Linda, CA, USA Lawrence D. Longo

References

Butterfield H (1965) The Whig interpretation of history. W.W. Norton, New York
Emerson RW (1883) Essays.... First and Second Series. A.L. Burt Co., New York
Kuhn TS (1962) The structure of scientific revolutions. University of Chicago Press, Chicago, IL Merton RK (1965) On the shoulders of giants. A Shandean Postscript. With a Foreword by C.D. Bowen. The Free Press, New York
Smith CA (1945) The physiology of the newborn infant. C.C. Thomas, Springfield, IL. 2nd edn, 1951; 3rd edn, 1959
White TH (1961) The making of the President, 1960. Atheneum Publishers, New York

Contents

1 Introduction 1
References 7

2 A Scientific Genealogy: Early Development of Fetal-Neonatal Research 9
2.1 The Beginnings and Some Definitions 9
2.2 Arthur St. George Huggett and Early Studies of Fetal Physiology 11
2.3 Late Nineteenth- and Early Twentieth-Century Contributions by German Physiologists and Others 13
2.4 Nicholson J. Eastman, Huggett, and Others of the 1930s to 1950s 18
2.5 Joseph Barcroft and a Widening of Interest in Physiology of the Fetus 25
References 39

3 Oxford and the Development of Physiology, with Notes on the Nuffield Institute for Medical Research 47
3.1 William Harvey and the Seventeenth-Century Physiology . . . 47
3.2 Other Early Oxford Physiologists 51
3.3 Founding of the Royal Society 54
3.4 The Oxford Medical School and Further Developments in Physiology 55
3.5 The Nuffield Institute for Medical Research 61
References 64

4 Geoffrey S. Dawes: A Life in Science 69
4.1 Early Life and Work 69
4.2 Dawes and the Fetal Cardiovascular System: The 1950s and 1960s 74
References 82

5 Fetal Asphyxia and the Primate Colony in Puerto Rico 85
5.1 Historical Perspective 85
5.2 Eastman and "Mt. Everest in Utero" 88
5.3 William F. Windle and the Primate Colony at *Cayo Santiago* 90
5.4 The Puerto Rico Studies of Asphyxia 91
5.5 Virginia Apgar and Evaluation of the Newborn Infant 95
5.6 In Summary 97
References 97

6 The Pulmonary Vasculature and Dawes' *Foetal and Neonatal Physiology* 103
6.1 The Pulmonary Vasculature of the Fetus and Newborn 103
6.2 Dawes' *Foetal and Neonatal Physiology* 112
References 114

7 Embryology and Early Developmental Physiology 119
7.1 Origins 119
7.2 Stazione Zoologica di Napoli 129
7.3 Embryology Becomes a Science 134
7.4 Franklin Paine Mall and the Carnegie Institution Department of Embryology 136
7.5 Other Early Twentieth-Century Developments in Embryology 139
References 145

8 Some Aspects of the Physiology of the Placenta 153
8.1 Late-Nineteenth and Early-Twentieth Centuries 153
8.2 Mid-Twentieth Century to the Present: Placental Fine Structure and Function 161
8.3 Some Aspects of the Uteroplacental Circulation and Transplacental Exchange 163
8.4 Pathology of the Placenta 178
8.5 The Human Placental Project 179
8.6 Summary and Conclusions 179
References 180

9 Some Aspects of Endocrinology of the Placenta 195
9.1 Introduction 195
9.2 Steroid Hormones 196
9.3 Polypeptide Hormones 202
9.4 Summary and Conclusions 207
References 208

10 Maternal Physiology of Pregnancy 217
10.1 Introduction 217
10.2 Frank E. Hytten and Early Studies on Maternal Physiology . . . 218

10.3 The Reproductive Tract in Pregnancy . . . 224
10.4 Maternal Metabolic Changes in Pregnancy . . . 227
10.5 Pregnancy-Associated Changes in the Endocrine System . . . 228
10.6 Cardiovascular System: Blood Volume . . . 235
10.7 Maternal Cardiac Output . . . 237
10.8 Arterial Blood Pressure . . . 239
10.9 Cardiovascular Hemodynamics of Pregnancy . . . 240
10.10 Uteroplacental Blood Flow . . . 241
10.11 The Respiratory System in Pregnancy . . . 245
10.12 The Kidneys and Urinary Tract in Pregnancy . . . 246
10.13 The Gastrointestinal Tract in Pregnancy . . . 248
10.14 Amniotic Fluid and Its Dynamics . . . 248
10.15 Uterine Contractions of Labor . . . 251
10.16 Summary . . . 262
References . . . 262

11 Maternal Complications of Pregnancy that Affect Fetal Development . . . 281
11.1 Premature Onset of Labor and Delivery . . . 281
11.2 Chorioamnionitis . . . 290
11.3 Obesity in Pregnancy . . . 292
11.4 Diabetes in Pregnancy . . . 302
11.5 Hypertension in Pregnancy: Preeclampsia/Eclampsia . . . 314
11.6 HELLP Syndrome . . . 330
11.7 Mental Health and Neuropsychiatric Issues . . . 335
References . . . 337

12 Fetal Growth and Its Restriction . . . 365
12.1 Early Studies . . . 365
12.2 Neonatal Birthweights, Fetal Growth Restriction, and the Small for Gestational Age Infant . . . 371
12.3 Further Perspectives on Fetal Growth Restriction . . . 378
12.4 Fetal Growth Restriction in Laboratory Animals . . . 381
12.5 Cardiovascular Function with Fetal Growth Restriction . . . 382
12.6 Fetal Growth Restriction and Neuropsychological Correlates . . . 385
12.7 Fetal Growth Restriction and the Placenta . . . 386
12.8 Fetal Growth Restriction and the Developmental Origins of Adult Health and Disease . . . 390
12.9 Conclusions with Perspective . . . 394
References . . . 395

13 Fetal-Neonatal Growth and Metabolism . . . 413
13.1 Robert A. McCance, Elsie May Widdowson, and Continued Studies of Growth and Metabolism . . . 413
13.2 Metabolic Rate . . . 419
References . . . 420

14 Fetal Growth Restriction at High Altitude: Clinical Observations 423
14.1 High-Altitude Long-Term Hypoxia and the Human Condition 423
14.2 The Colorado and Mountain States Studies 424
14.3 Clinical Studies from the *altiplano* of South America 426
14.4 The Relation of Birthweight to Gestational Age 428
14.5 Translational Studies of Pregnancy at High Altitude 429
14.6 High Altitude and the Placenta 430
14.7 Conclusions with Perspectives 431
References 432

15 Fetal Growth Restriction at High Altitude: Basic Cellular and Subcellular Physiologic Considerations 435
15.1 Pregnancy and High-Altitude, Long-Term Hypoxia 435
15.2 Interrelations of Fetal Blood O_2 Affinity and Capacity with that of the Mother 444
15.3 Initial High-Altitude Studies on the Peruvian *Altiplano* 445
15.4 Studies in Sheep Subjected to Hypobaric Hypoxia 451
15.5 Cardiovascular Studies in the Chick Embryo 453
15.6 Studies of Prolonged Hypoxia in Rodents 454
15.7 Studies in Sheep Acclimatized to High Altitude at the White Mountain Research Station 455
15.8 Further Sheep Studies on the *Altiplano* 457
15.9 Fetal Cardiovascular Responses to Long-Term Hypoxia 458
15.10 Fetal Coronary Vascular Responses 461
15.11 Fetal Cerebrovascular Responses to Long-Term Hypoxia . . . 462
15.12 Some Aspects of Cardiovascular Function in the Llama Fetus 470
15.13 Long-Term Hypoxia and the Fetal Hypothalamic-Pituitary-Adrenal Axis 472
15.14 Fetal Metabolic Responses to LTH 473
15.15 Hypoxia-Mediated FGR and Neuropsychological Correlates . . . 475
15.16 High Altitude and the Placenta 476
15.17 Conclusions with Perspectives 480
References 483

16 Epigenetics and the Fetal Origins of Adult Health and Disease . . . 501
16.1 Overview 501
16.2 A Brief Introduction to Epigenetics and Development 502
16.3 The Dutch "Hunger Winter" of 1944–1945: A Case Study . . . 506
16.3.1 Maternal and Infant Characteristics 506
16.3.2 Metabolic Sequelae 508
16.3.3 Cardiovascular Sequelae 509
16.3.4 Related Sequelae 510
16.3.5 Neuropsychological Sequelae 511

16.4 Other Antenatal Maternal Starvation Studies . . . 513
16.5 A Perspective on the Fetal Origins of Adult Health and Disease . . . 513
16.6 Critiques of the "Fetal Origin" Hypothesis . . . 519
16.7 Malnutrition During Pregnancy as a Global Health Problem . . 521
16.8 Further Questions to Consider . . . 522
References . . . 523

17 Some Aspects of the Developing Brain and Nervous System . . . 535
17.1 Overview . . . 535
17.2 Developmental Neurogenesis . . . 538
17.3 Cognitive Development . . . 541
17.4 Cerebral Blood Flow in the Fetus and Newborn . . . 545
References . . . 549

18 Related Developments in Fetal and Neonatal Endocrinology . . . 557
18.1 The Beginnings of Reproductive Endocrinology and Medicine . . . 558
18.2 Fetal-Neonatal Endocrinology . . . 559
18.3 Developmental Neuroendocrinology . . . 563
18.4 Hormonal Regulation of the Timing of Birth . . . 567
References . . . 571

19 Further Developments in Fetal and Neonatal Physiology . . . 581
19.1 Pulmonary Physiology and Respiratory Distress Syndrome . . 581
19.2 Corticosteroids and Maturation of the Fetal Lung . . . 593
19.3 A Tribute to "Mont" Liggins . . . 598
19.4 Blood and Hematology . . . 601
19.5 Hyperbilirubinemia and Kernicterus in the Fetus and Newborn . . . 605
19.6 Immunology . . . 607
19.7 Chronic Catheterization of the Fetus . . . 609
19.8 Cardiovascular Physiology . . . 612
19.9 Related Fields of Research . . . 614
References . . . 614

20 Additional Clinical Aspects of Developmental Physiology and Clinical Care . . . 631
20.1 Neonatal Intensive Care in Preterm Birth . . . 631
20.2 Retinopathy of Prematurity . . . 643
20.3 Transcutaneous O_2 Measurements . . . 647
20.4 Thermoregulation . . . 649
20.5 Some Aspects of the Development of Maternal-Fetal Medicine . . . 651
20.6 Some Aspects of Newborn and Child Care . . . 656
20.7 Pathology of the Fetus and Newborn . . . 658
References . . . 659

21 Governmental Support of Research in Fetal and Newborn Physiology 673
21.1 The Medical Research Council of Great Britain 673
21.2 The Medical Research Councils of Canada and Australia 677
21.3 The US National Institutes of Health 678
References 688

22 Bioethical Issues in Research on the Fetus and Newborn Infant . . . 691
22.1 An Awakening of Responsibility 691
22.2 The Emergence of Bioethics 693
22.3 The Massachusetts Experience 694
22.4 Later Developments 696
References 698

23 Textbooks, Monographs, and Other Volumes on Fetal and Newborn Physiology 703
23.1 Volumes on Physiology of the Fetus and Newborn Infant . . . 703
23.2 The Josiah Macy, Jr. Foundation Conferences on Gestation . . 708
23.3 New York Academy of Sciences Conferences on Fetal Homeostasis 710
23.4 Essays in Perinatal Medicine 711
References 712

24 Fetal "Breathing" in the 1970s and Fetal Heart Rate Analysis in the 1980s and Early 1990s 715
24.1 Early Studies of Fetal Breathing Movements 715
24.2 Fetal Breathing in Humans 722
24.3 Early History of Fetal Heart Rate Monitoring 724
24.4 Subsequent Studies on Electronic Fetal Heart Rate Monitoring 728
24.5 Some Contemporary Developments 731
References 734

25 Dawes' Contributions to Symposia and a Summing Up 745
25.1 Ciba Foundation Symposia 746
25.2 The Barcroft Centenary Symposium 749
25.3 The "Dawes Symposium" and Others 750
25.4 A Summing Up by Dawes 752
References 754

26 Dawes as a Mentor: Reminisces of Former Graduate Students, Postdoctoral Fellows, and Associates 757
References 781

27 Early Years of the Society for Reproductive Investigation (Formerly Society for Gynecologic Investigation), the Fetal and Neonatal Physiological Society, and Several Other Groups 783
27.1 Beginnings of the Society for Gynecologic Investigation, Now Society for Reproductive Investigation 784
27.2 Journal of Gynecologic Investigation/Reproductive Sciences 785
27.3 The Fetal and Neonatal Physiological Society 790
References 796

28 The Reproductive Scientist Development Program and Related Programs 797
28.1 Introduction 797
28.2 The Reproductive Scientist Development Program 798
28.3 Some Personal Reminisces 799
28.4 A Meeting of the Selection Committee 804
28.5 Further Reminisces 811
28.6 The Naftolin Excellence in Mentorship Award 811
28.7 Perspectives of Several RSDP Scholars' Reports 814
28.8 Other Education Awards in Obstetrics and Gynecology 818
28.9 The Pediatric Scientist Development Program (PSDP) 819
References 820

29 Epilogue 821
29.1 The Adventure of Science 821
29.2 Fundamental Research, Clinical Medicine, and the Role of the Physician-Scientist 828
29.3 Fetal and Neonatal Physiology and Its Relation to Physiology in General 830
29.4 Fetal-Neonatal Physiology and the Future 832
29.5 What Lessons Are to Be Learned? 833
29.6 Conclusion 839
References 840

Bibliography of Geoffrey S. Dawes 843

Chapter 1
Introduction

> *Some Divines count* Adam 30. *yeares old at his creation, because they suppose him created in the perfect age and stature of man; and surely we are all out of the computation of our age, and every man is some moneths elder than hee bethinks him; for we live, move, have a being, and are subject to the actions of the elements, and the malice of diseases, in that other world, the truest Microcosm, the wombe of our mother. . .. In that obscure World. . ., our time is short, computed by the Moone; yet longer than the days of many creatures that behold the Sunne, our selves being not yet without life, sense, and reason; though for the manifestation of its actions, it awaits the opportunity of objects; and seemes to live there but in its roote and soule of vegetation: entring afterwards upon the scene of the world, wee arise up and become another creature. . ..*
>
> (Sir Thomas Browne 1642, 1964, p. 38)

In his "Thoughts on the evolution of a scientific problem," Sir Cyril Norman Hinshelwood (1897–1967), Dr. Lee's Professor of Chemistry and Fellow of Exeter College, Oxford, in this 1953 Presidential Address to the Science Masters' Association of Oxford University, observed "the scientific aspiration towards the understanding of Nature represents one of the great movements of the human mind. . .." (Hinshelwood 1954, p. 300). Hinshelwood wisely noted, "Science is not the dryly syllogistic handling of obvious facts. It is an imaginative adventure of the mind seeking truth in a world of mystery." He continued, ". . . and, as it happens, one of the most important steps is almost always that made by people who have the vision to realize that certain phenomena raise questions of unusual interest. And it may be that the first tentative answers to these questions go further along the road than the latter amendments simply because they provide the motive and occasion for the key discoveries" (Hinshelwood 1954, pp. 300–301). A decade later in his 1965 Presidential Address to the British Association for the Advancement of Science, Hinshelwood noted that "at all the boundaries of science we come up against what are probably the inherent limitations of human understanding. At the edge of biology we meet the chasm between what science describes and what the mind

L.D. Longo, *The Rise of Fetal and Neonatal Physiology*, Perspectives in Physiology,
https://doi.org/10.1007/978-1-4939-7483-2_1

experiences…" (Hinshelwood 1965, p. 355). George Santayana (1863–1952) observed, "Science is nothing but developed perception, integrated intent, common sense rounded out and minutely articulated" (Santayana 1906, p. 307), and Sir Winston Leonard Spencer Churchill (1874–1965) is alleged to have echoed a somewhat similar theme in a lighter manner, "Science is no more than organized curiosity" (Priestley 1957, p. 148).

Science also has been defined as the observation, identification, description, experimental investigation, and theoretical explanation of natural phenomena. As an intellectual exercise, it continues to expand, both in breadth of inquiry and in the depth to which questions are explored. Science extends from the outer limits of cosmology to the molecular, atomic, and subatomic basis of existence. The Latin word *scientia* is derived from *sciens* the past participle of *scire*, to know. As stressed by George Alfred Leon Sarton (1884–1956) of the Johns Hopkins University, science is the only field of intellectual activity that is progressive (Sarton 1927–1948, 1937, 1952). He later reemphasized this view:

> The history of science may be defined as the story of the gradual unveiling of objective truth and of the conquest of matter by mind, it describes the age long and endless struggle for freedom of thought … .. The history of science is one of the essential parts of the spiritual history of mankind, the other main parts being the history of art and of religion. It is not more important or more enlightening than these other parts, but it differs from them in that the development of knowledge is truly cumulative and progressive … if we would explain the progress of mankind, the history of science should be the very axis of our explanation.
> (Sarton 1957, pp. 1–2)

Midway between the extremes of the infinitesimally minute subnuclear particle to that of the infinitesimally expansive cosmos is the human being, *Homo sapiens*, that sentient creature that observes, contemplates, questions, and wonders. As the study of vital life processes and functions, the discipline of physiology (from the Greek *physis* "nature" or "origin" and *logia* "the word" or "study of") lies at the core of an integrated understanding of biological function. Unique among the biomedical sciences, physiology is the study of the dynamics of life, describing the vital functions of living organisms, their tissues, and cells. As a consummate example of reductionism, the science of physiology includes integrative function of the whole body and its system organs, cells, and molecules. That is, critical to a reductionist approach is that of integration of the sum of the parts into a greater, global view of the body. Claude Bernard (1813–1878), the great nineteenth-century Parisian biologist-physiologist, was an articulate proponent of this concept. Among his contributions, he asserted the integral importance of the *milieu intérieur* [internal environment] and the role of physiologic functions in maintaining the constancy of organs and their constituents (Bernard 1878). In his *The wisdom of the body*, Walter Bradford Cannon (1871–1945) championed the view of homeostasis of the *milieu intérieur* (Cannon 1932).

From the standpoint of ontogeny, one can inquire into the critical features of development and their functional capabilities that give rise to the individual being who can utilize his/her endowment, gifts, and abilities, to experience a full life, living, loving, cherishing, and contributing. This constitutes the republic of fetal and neonatal physiology. Although limited, in terms of the planetary systems,

galaxies, and expanding universe of science, the field of developmental physiology goes back several centuries. In this synopsis, I would like to consider some aspects of this history as a case study. That is, the manner in which, with sequential and parallel discoveries, persons of more than average ability came together, bringing their different backgrounds, talents, and expertise, to ask critical questions. And by diligence and persistence, often in the face of adversity and not necessarily in agreement, these individuals innovated, developing unique models, and opened new vistas to explore. With these contributions, novel ways of thinking occurred in reasoning and reflection upon a given subject that in many instances contributed to advances in care of the pregnant mother and newborn infant. As acknowledged by others, history is difficult to evaluate, even with the availability of well-documented records. Its exploration has a way of keeping us humble. In interpreting historical events and phenomena, it is important to attempt to know the mind-set and goals of those involved. Thus, in the present survey, insofar as possible I have attempted to enlist and record the opinions of the key investigators in the evolution of this field.

By definition, fetal and neonatal physiology encompasses events from early embryonic development through full development of the fetus, and includes the profound changes at the time of birth, and the first month of life as a newborn infant. Growth and development are a function of both genetic and environmental factors, and these represent a continuum of change that serves to maintain homeostasis of the organism. As an example, the history of research on the fetal circulation, which is valid for the field of fetal physiology in general, has been divided into four eras: the anatomical period from the time of Galen [Claudius Galenus] (131–201 CE) of Pergamum [also Pergamon], those contributions from the time of William Harvey (1578–1657) onward, the period of anatomy and anatomical-based physiological hypotheses, and the era of hypothesis-based experimental research which commenced in the mid to late nineteenth century (for instance, see Barclay et al. 1944).

In addition to increasing basic understanding of fundamental physiologic, biochemical, molecular mechanisms, a critical aspect of advances in fetal and neonatal physiology has been its many contributions to clinical medicine, both obstetrical perinatology and pediatric neonatology. It is by such research that patient care for the gravid mother, fetus, and newborn infant have advanced beyond blind empiricism. Importantly, the field is a model of translational biomedical science at its best. As suggested by the subtitle, beyond its contributions to basic science, fetal and neonatal physiology is exemplary in serving as a bridge "from bench to bedside," to advance clinical care. In an attempt to present some of the advances in translational/clinical science, and to engage a broad audience, from undergraduate to graduate students, medical students to practicing physicians, I have included a number of related contributions in reproductive medicine such as development of the fetal/newborn brain, endocrinology, and pulmonary and cardiovascular biology. With the wide interests of a diverse readership, the volume is organized so that one may select those chapters relevant to ones interests.

In general, major contributions to science, the humanities, the arts, and other areas of knowledge have originated from two processes. The first is conceptual. The polymath Arthur Koestler (1905–1983), in his *The Act of Creation*, described this as

"the bisociation" of two ideas or areas of knowledge, which previously had not been appreciated to be related, igniting the mind of an original thinker. On occasion, such associations may occur in an instant (Koestler 1964). The second is the detailed, laborious, experimental testing of a new, innovative concept or hypothesis in an effort to obtain the evidence that either will support or refute a given idea or question. This stage may take years or decades. In speaking of art and its genesis, Walter Gropius (1883–1969) who forged the utilitarian movement in architecture and fine art known as *Bauhaus* [house of building/building school], observed that art blossoms in rare moments of inspiration by the grace of heaven (Gropius 1970). The same may be said for creative, innovative science.

In physiology, and almost all areas of the biomedical sciences, study of the adult organism has preceded that of the fetus or newborn infant. In fetal and neonatal physiology, the majority of contributions have appropriated major conceptual breakthroughs from general biology, biochemistry, or physiology and applied them to the developing organism. Because the fetus is, in effect, an "astronaut in utero," and the newborn infant, particularly one that is markedly premature, is such a fragile organism, experimental studies to uncover fundamental mechanisms have been neither easy nor straightforward. Thus, the field has been met with challenges from almost every quarter. As the English poet and critic Samuel Taylor Coleridge (1772–1834) observed, "The history of a man for the 9 months preceding his birth, would, probably, be far more interesting, and contain events of far greater moment than all the three-score and 10 years that follow it" (Coleridge 1836, p. 244). And as in his poem "C.L.M." regarding our antenatal experience, John Masefield (1878–1967) wrote:

> In the dark womb where I began
> My mother's life made me a man.
> Through all the months of human birth
> Her beauty fed my common earth.
> I cannot see, nor breathe, nor stir
> But through the death of some of her.
> (Masefield 1927, p. 77)

Fundamentally, scientific research looks to the future, to discover what can be imagined and discovered. And yet there is no escaping its history. Perhaps more than in other pursuits of the intellect, that which is possible in science critically depends upon what has been. Of importance in this regard are not only the facts that have been discovered but also the inspiration to be gained and the appreciation of the achievements of those who have gone before. At the same time science lays bare the paucity of our knowledge. Oliver Wendell Holmes (1809–1894), Professor of Anatomy at the Harvard Medical School, recognized this in his essay "Border Lines of Knowledge in Medical Science." He wrote, "Science is the topography of ignorance: From a few elevated points we triangulate vast spaces, inclosing infinite unknown details …. The best part of knowledge is that which teaches us where knowledge leaves off and ignorance begins" (Holmes 1891, p. 211).

An ineluctable consequence of the growth of science is that in essentially every field of inquiry, as it becomes established the subjects expand, become increasingly

complex, and divide into further subdisciplines. In part, reflecting intellectual insights, this process of fracture is a consequence of discoveries and advancements in technology and instrumentation. In the late nineteenth century, Thomas Henry Huxley (1825–1895) one of the founders of the Physiological Society in the United Kingdom, foresaw the inevitability of reductionism when he observed that it would appear that, "... the scientific, like other revolutions, meant to devour its own children; as if the growth of science tended to overwhelm its votaries; as if the man of science of the future were condemned to diminish into a narrow specialist as time goes on" (Huxley 1864; Bibby 1967, p. 234). In considering special features of biological science, Huxley observed, "... Physiology is *the* experimental science *par excellence* of all sciences; ... that which affords the greatest field for the exercise of those faculties which characterize the experimental philosopher ..." (Huxley 1864; Bibby 1967, pp. 53–54).

In this volume, I have striven to chronicle those discoveries and related matters of most importance and relevance. Although attempting to remain free of bias and give full justice to every vital contribution, I appreciate that as a lone author my perspective is less than perfect. What follows is a singular view of the antecedents of this field of physiology, that of the fetus and newborn infant. In particular, for his role as a catalyst and synthesizer, I detail many aspects of the role of the Oxford pharmacologist-physiologist Geoffrey S. Dawes who worked to develop and mature this intellectual endeavor. As a pioneer who donned the mantle of his predecessors, by his indefatigable labors, Dawes not only personally advanced the science but also did so through the influence of the scholars who worked with him, many of whom went on to distinguished careers at academic centers throughout the world.

Some have viewed the origin of this field in terms of a "big bang" theory, e.g., that it commenced in a blinding flash of academic brilliance at the Nuffield Institute in the early 1950s. As this review documents, that is not quite the case. Albeit, although this subspecialty of physiology matured during this period, its creation and development is a long and complex story. In addition to many only minor breakthroughs, it includes digressions and side roads, blind alleys and dead ends, incorrect ideas, and often some degree of confusion and differing perspectives.

The fetus has been viewed from many perspectives. In 1916, Armenouhie Tashjian Lamson, (1887–1970) the physician director of a free prenatal clinic in Seattle, Washington, published *My Birth: The Autobiography of an Unborn Infant*, a chronicle of her unborn infant's 9-month struggle to develop from a fertilized ovum to an embryo, fetus, and newly born son (Lamson 1916). The narrator, Lamson's fetus, stressed the importance of good food and a salutary environment not only in supporting his growth and development but also that of America as a nation. Lamson used her story of embryonic/fetal development as a commentary on the era in which increasing industrialization, economic influence, immigration, and professionalization were reshaping cultural and intellectual life, social structures, and the political economy of the country. During the course of the twentieth century, the "new fetus" became an entity/persona of considerable cultural influence. In her foreword, regarding this antenatal period Lamson reassured, "knowledge will fill every minute of that person with happiness and a peace that comes only from perfect understanding" (Lamson 1916, p. 7).