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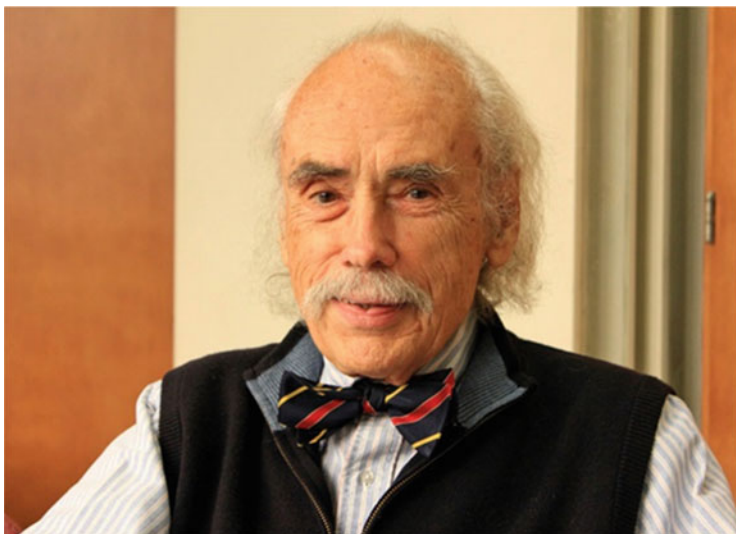
## Perspectives in Physiology

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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



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# 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 through 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.

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# 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.

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# 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 incognita* 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 incognita*. 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.

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