Fetal and Newborn Cardiovascular Physiology

Volume 1 Developmental Aspects

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Preface

In his monumental description of the circulation of the blood, *Exercitatio anatomica de motu cordis et sanguinis in animalibus* (Francofurti, sumpt. G. Fitzeri, 1628), William Harvey first described the circulation of the fetus as well as that of the adult. He used the example of the fetal heart to bolster his argument that the blood passes from the right to the left heart through the pulmonary vascular bed rather than through invisible pores in the septum of the heart. Harvey observed that

> . . . there is absolute identity between what happens in the human embryo and what happens in others, in which the unions in question are not in process of abolition. Hence, the heart, by its movement, transfers blood very freely from the vena cava, through both ventricular conduits, into the great artery [aorta]. The

> right ventricle receives blood from the auricle and then drives it forward through the artery-like vein pulmonary artery and its offshoot, the so-called artery-like channel [ductus arteriosus], into the great artery. The left ventricle, in like manner, simultaneously receives blood, that has been directed from the vena cava, by a different route, through the oval opening [foramen ovale], by means of the auricular movement, and by its tension and contraction it drives this blood through the root of the aorta into the same great artery. Thus, in the embryo, while the lungs are idle and devoid of activity or movement, as though they did not exist, Nature uses the two ventricles of the heart as one for the transmission of the blood.

Of course, the unique anatomical features of the fetal circulation had been described long before Harvey's time. For instance, Galen first described the foramen ovale and the ductus arteriosus (*Opera omnia*. Ediderunt Andreas Asulanus et J. B. Opizo. Venetiis in aedibus Aldi . . . , 1525), and Vesalius apparently first described the ductus venosus in a work published posthumously (*Anatomicarum Gabrielis Falloppii observationum examen* . . . , Venetiis, Apud Franciscum de Franciscis, Senensem, 1564).

Modern knowledge of the fetal circulation, however, originated to a great extent with two groups of investigators. In 1927 Huggett determined that the oxygen affinity of blood of the fetal goat differed from that of its mother. Although we know that Huggett's oxyhemoglobin dissociation curves were incorrect, his conclusions stimulated other workers to determine these interrelations under various circumstances and tease out the mechanisms of this phenomenon. A decade later, Sir Joseph Barcroft, Donald H. Barron, Alfred E. Barclay, and Kenneth J. Franklin used cineangiography to demonstrate for the first time the circulation of the intact fetus delivered by Cesarean section. Using this technique, these workers also first demonstrated the time of functional closure of the ductus arteriosus.

Several previous monographs have been devoted to the circulation of the fetus and/or the newborn. These include *The Foetal Circulation and Cardiovascular System, and the Changes They Undergo at Birth* by Barclay, Franklin, and

Prichard (1944); Sir Joseph Barcroft's, *Researches on Prenatal Life* (1946); the work of Lind, Stern, and Wegelius, *Human Foetal and Neonatal Circulation* (1964; an essentially new and much expanded edition, edited by Walsh, Meyer, and Lind, appeared in 1974); Cassel's *The Ductus Arteriosus* (1973), and *The Heart and Circulation in the Newborn and Infant* (1966); and most recently, Rudolph's *Congenital Diseases of the Heart* (1974). Each of these volumes presents a reasonably complete account of the major morphologic features of the heart and great vessels and the physiologic aspects of the fetal and/or newborn circulation. In addition, several of these works review *in extenso* congenital heart disease and other clinical aspects of the circulation.

During the past decade an increasing number of investigators have attempted to elucidate the ontogeny of the control mechanisms during development of the circulation in the fetus and newborn. They have probed such areas of investigation as the development of baroreceptors and chemoreceptors in autonomic control, the control of cardiac output and distribution of blood flow to the peripheral tissues, the control of blood flow through the ductus arteriosus, the factors that determine the mean blood pressure or blood pressure set point, and the effects of hypoxia in the fetus and newborn infant.

The titles of the papers in this monograph reflect some of the recent progress in understanding these and related problems. Because of the interdisciplinary nature of this field of research, and the fact that many individuals working in related areas present their work at different meetings of different societies and so may be unaware of one another's work, we organized a symposium at which investigators not only could present their newest and exciting work, but could interact and share ideas. This symposium was held 11 to 14 August 1976 in Bryn Mawr, Pennsylvania, in conjunction with the fall meeting of the American Physiological Society. About 90 investigators from 11 countries gathered to test their ideas on one another.

Because of his contributions to this field, the conference and these volumes are dedicated to Donald H. Barron. A high point of the symposium was a banquet Thursday evening, 13 August. Donald Barron spoke on "From Harvey's Question (1651) to Zweiffel's Answer (1876)."

Following this presentation, a number of Dr. Barron's friends and former colleagues reviewed his contributions to science and his influence on their lives. Dr. Barron's paper, and some reminiscences by Samuel R. M. Reynolds, constitute the introductory section to this volume.

The next section considers some developmental aspects of the fetal and neonatal cardiovascular system. Assali and his colleagues present an overview of the fetal response to autonomic sympathetic and parasympathetic pharmacologic agents and the changes that occur in the fetal responses during maturation. Gootman et al. investigate postnatal maturation by stimulation of afferent nerves or the central nervous system directly, in addition to examining the interactions of these systems and the effects on them of pharmacologic agents. Van Petten et al. further explore the time course of vascular responses to adrenergic drugs, the development of presynaptic nerves, and the development of the receptor-effector system in the fetus and newborn. Su et al. document the difference in the developmental pattern of the adrenergic neuro-effector synapse in various blood vessels of the fetus. Sperelakis and McLean note the striking changes that occur in the electrical properties of myocardial cells during embryonic development, while Lieberman et al. review some problems associated with electrophysiologic studies of these embryonic myocardial cells. Some unique features of the metabolic maturation of the fetal heart are reported by Wildenthal and by Beatty and her colleagues.

In the following section several workers consider different aspects of the control of cardiac output. Gilbert discusses venous return and role of mean systemic pressure and vascular compliance in the control of cardiac output. Power et al. hypothesize on the role of the relative concentrations of carbon dioxide and bicarbonate ion, amino acids, and glucose in regulating placental transcapillary water exchange and fetal blood volume, and thus cardiac output; and Longo et al. consider the interrelations of blood volume and extracellular fluid volumes and the role of blood volume in the regulation of fetal cardiac output. Kirkpatrick and Friedman examine the problem of whether the Frank-Starling relation operates in the fetus and discuss the role of the changing myocardial fiber length in determining the cardiac output. Maylie et al. suggest that ultrastructural development of the myocardial T-tubular system and sarcoplasmic reticulum determines the force-fre-

quency relations of the developing heart. Versprille et al. present a morphologic analysis of the developing heart that correlates ventricular geometry with function. Mott reviews the development of the renin-angiotensin system in the fetus and its role in regulation of extracellular fluid volume and vasomotor tone.

An exciting development--both from the standpoint of understanding the control of blood flow through the ductus arteriosus and great vessels of the fetal heart, and its implications in the treatment of newborn infants with certain congenital heart defects--is the discovery of the role of prostaglandins and related hormones in the fetal and neonatal circulation. Cassin et al. analyze the role of prostaglandins in the control of the developing pulmonary circulation, and Friedman and Kirkpatrick present the therapeutic uses of prostaglandins in closure of the ductus arteriosus. Both M. A. Heymann (University of California, San Francisco) and F. Coceani (Hospital for Sick Children, Toronto, Canada) also participated in this session of the symposium; however, their discussions are not included. Finally, Rankin presents an interesting hypothesis on the role of prostaglandins in regulating maternal and fetal placental blood flows.

The first volume closes with some theoretical considerations. Although physics and mathematics have strong mathematical underpinnings, too often biologists have been content to gather data and perform experiments with little appreciation of the theoretical aspects of a given problem. Fortunately, mathematical approaches are being used increasingly in an attempt to understand certain aspects of the circulation and respiratory gas transport in the fetus and newborn. Cameron et al. present a thorough mathematical analysis using a deterministic, lumped parameter formulation of the fetal circulation. Allen and his colleagues develop a somewhat different approach for studying the time course and magnitude of changes of oxygen levels in response to hypoxia. Butler et al. present a theoretical consideration of maternal and fetal placental blood flows during uterine contractions and the implications on transplacental oxygen exchange. Both Veth and van Bemmel, and Gibbons et al. present a mathematical basis for interpreting some of the changes in fetal heart rates observed during labor and delivery.

Volume II considers several aspects of the peripheral circulation in the fetus and newborn infant. Numerous questions relate to the regulation of the fetal umbilical circulation and the control of the fraction of cardiac output perfusing the placenta during development from a minute embryo, in which almost all of the output from the heart goes to the placenta, to a near-term fetus, in which this fraction decreases to about 50% of total cardiac output. This control probably involves not only adrenergic agents as discussed by Chez et al. and Tulenko, but also the respiratory gases in blood as reported by Motoyama et al. Reynolds compares the fetal umbilical circulation to a pulsometer pump, while Bissonnette examines the problem of recruitment versus distension and the regulation of volume of the placental capillaries.

Obviously the ultimate purpose of the evolving circulation is to deliver adequate oxygen and other nutrients to, and catabolites from, the cells of developing tissues. Mela et al. review some unique features of fetal mitochondria during the perinatal period, such as changes in the concentration of cytochromes, their turnover rate and rate of respiration. Using microelectrodes, Silver compares the oxygen tensions and the pattern of electrical discharge during normoxia and hypoxia in several areas of the fetal and adult brain. In turn, Erdmann presents the oxygen tension response of these cells when anesthetic agents are administered to the mother. In contrast to the brain and other organs, the fetal liver is supplied with blood of widely varying oxygen tension. The left physiologic lobe is perfused with blood (from the umbilical vein) with a relatively high oxygen tension, while the right physiologic lobe receives blood (from the portal vein) at a relatively low oxygen tension. Dvorchik compares the distribution of some components of the mixed-function oxidase system with the fetal hepatic circulation and hepatic oxygenation. Caton et al. demonstrate that factors other than just fetal mass determine the rate of oxygen consumption by the fetus. Barker analyzes the role of blood flow in determining the genesis and growth of the cerebral microcirculation during development. Abrams et al. use recently developed thermal techniques to calculate fetal cerebral blood flow under a variety of conditions. Schreiner and his colleagues study the preferential utilization of various substrates by the fetus of fed and fasting sheep.

Manifestly, hypoxia can affect the circulation of the fetus and newborn infant; however, one cannot extrapolate from hypoxic effects in the adult to the qualitative or quantitative effects in the fetus or newborn infant. Dawes reviews some of the problems associated with circulatory studies in the chronically catheterized lamb fetus. Several caveats he notes in working with these preparations concern cyclical variations in fetal heart rates, blood gases, breathing movements, and lability due to noise or maternal stress. Parer demonstrates that fetal oxygen consumption is a function of arterial oxygen tension, and Cohn et al. present data on the role of the autonomic nervous system and the redistribution of blood flows during hypoxia. Longo and co-workers compare the fetal circulatory response to hypoxia induced by breathing low oxygen mixtures and that associated with carbon monoxide. The effects of partial umbilical cord compression (Towell and Lysak) or complete occlusion (Künzel et al.) are reviewed. Mann et al. analyze the fetal electroencephalographic and metabolic response to graded hypoxia, while Brotman et al. present the effects of prenatal or postnatal hypoxia on brain biogenic amines and other neurotransmitters. Ferguson and his colleagues describe the redistribution of blood flow in newborn lambs following exchange transfusion; and Anday et al. contrast the cardiovascular response of low birth weight infants to exchange transfusion with fresh packed erythrocytes to that with whole blood. Pernoll et al. examine the effects of maternal exercise on maternal and fetal heart rates and blood pressure. Elsner makes a fascinating comparison of the fetal cardiovascular responses in the deep-water diving mammal (seal) and terrestrial animal (sheep). Quilligan explores the problem of the extent to which fetal heart rates reflect fetal oxygenation.

Of course, a vital link in the chain of an adequate supply of oxygen and other nutrients for the fetal circulation to transport is that of placental exchange. Fuller and her co-workers demonstrate that the elusive perfused uterine preparation for experimental studies is indeed a reality. Gurtner and Burns discuss the hypothesis of carrier-mediated respiratory gas exchange in the placenta and present evidence that fulfills certain of their criteria for facilitated transport. Thornburg and Faber clarify the role of the various cells layers of the placental membrane as resistances to diffusion, while Boyd et al. present data

on the placental permeability to a number of solutes and discuss the implications of these permeabilities on the fluxes of various ions and solutes. Holland measures the reaction rate of carbon dioxide with the hemoglobin in both maternal and fetal erythrocytes, and discusses the implications of these reaction rates on placental respiratory gas exchange. Finally, Gautieri and Wolstenholme discuss the effects of various drugs on uterine and umbilical blood flow in the placental vasculature.

Perhaps several caveats should be noted. The overriding purpose of these volumes is to present some of the latest and best studies that are being carried out in various laboratories around the world toward an understanding of important physiologic problems in the circulation of the developing fetus and newborn. Little is presented on the anatomy and morphology of the fetal circulation or the specific changes that occur during birth. These topics are dealt with *in extenso* in other monographs and texts. Of necessity, most of the experiments reported in this monograph were performed in lambs, goats, monkeys, chicks, or other species. Obviously, the functional demands on the developing human circulation differ from those in various animals. For instance, the blood flow to the brain of a human near-term fetus or infant will be several times that of the blood flow to the lamb. On the other hand, there are many aspects of the circulation in both that are comparable, and these should not be overlooked. To a certain extent, the major divisions of the monograph are somewhat arbitrary. Several of the manuscripts could have been included in sections other than those in which they appear. However, we have attempted to group the papers so that each section will be as logically coherent as possible. Much of the data presented here is, as in most of science, reductionist and analytic in approach; that is, systems are dissected into smaller and finer bits and pieces. Unfortunately, we seem to pay too little attention to the other possible approach, that is, to synthesizing the bits and pieces again into an understandable system and integrated whole.

Finally, many of the studies are concerned with an understanding of fundamental biologic problems and may have little apparent relevance to clinical problems or disease. We are reminded of the words of Severinus (seventh century)

who wrote: "Go my sons, buy stout shoes, climb the mountains, search . . . the deep recesses of the earth . . . In this way and in no other will you arrive at a knowledge of nature and the properties of things." The path to deep understanding and insight winds through the jagged peaks of science rather than across the broad plains of technology. While some governmental administrations might wish to avoid this tortuous path by short cuts, there is, unfortunately, no "yellow brick road" to some scientific "Oz." Rather, our understanding will increase only as first-rate pioneers continue to explore the frontiers. Since the time of William Harvey it has become increasingly apparent that development of the heart during the perinatal period has a profound effect not only on the heart itself, but on the person as a whole.

Lawrence D. Longo