A Personal View of Neonatal Pulmonary Hypertension

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...in the embryo...the two ventricles
...as in a double nut...are nearly
equal in all respects...And this is
so, because in the fetus...blood...
flows by the foramen ovale and ductus arteriosus directly from the vena
cava into the aorta, whence it is distributed to the whole body. Both ventricles have therefore the same office
to perform, whence their equality of constitution. It is only when the
lungs are used, and it is requisite that the passages indicated should be
blocked up, that the difference...of strength...between the two ventricles begins to be apparent. In the altered circumstances, the right has
only to drive the blood through the lungs, whilst the left has to propel it through the whole body.
—William Harvey, 1628

Life takes unexpected turns. When I came to Denver in June 1957 to learn clinical cardiology from Gil Blount, my plan had been to spend one year at the University of Colorado and then return to my home in Hazard, Kentucky, to take up the practice of medicine. However, one reason I began a fellowship was to see what research might be like. I had always liked science, and my B.S. degree in biology from MIT had reflected a heavily scientific curriculum. In view of that back-

ground, Gil assigned me to the cardiac catheterization laboratory rather than to the clinical cardiology service. The assignment meant that I would work under the direction of Bob Grover, the newly appointed head of the laboratory. Out of the opportunity to work with Bob grew an enduring friendship, and the excitement of the laboratory changed the direction of my life. I would no longer pursue my plan of returning to the Appalachian region of Kentucky to practice internal medicine and cardiology.

Gil's practice included infants and children. One of the first catheterizations in which I participated was in J. J., a 14-month-old child with ventricular septal defect and pulmonary hypertension. Bob had been finding that tolazoline (an imidazoline with sympatholytic, parasympathomimetic, and histaminelike actions) lowered pulmonary arterial pressure and caused pulmonary vasodilation in young children and some infants such as J. J.\(^\text{19}\) (Fig. 1). It was known that pulmonary arterial pressure could be lowered by a pharmacologic agent,\(^\text{15,18}\) but studies like those in J. J. seemed important because they were showing for the first time that vasoconstriction contributed to pulmonary hypertension in congenital heart disease.

Our excitement was tempered by findings from sea level that tolazoline was ineffective in pulmonary hypertensive children with ventricular septal defects.\(^\text{32}\) One possibility was that the lower barometric pressure (\(P_B\), 630 mmHg) at Denver's altitude (1,600 m) was causing pulmonary vasoconstriction not present at sea level and that the tolazoline was reversing this constrictive component. The inspired oxygen tension in Denver is 122 mmHg compared to 150 mmHg at sea level. In infants with increased lung blood flows, the lower oxygen levels could cause the small pulmonary arteries to constrict.

A decade earlier, U. S. von Euler (Fig. 2) had shown that hypoxia caused pulmonary vasoconstriction in adult cats (Fig. 3). The discussion section in his paper addressed the question of the "purpose" of a pulmonary vasoconstriction by low oxygen. Those who are afraid it is not appro-

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**Figure 1.** Femoral and pulmonary arterial pressures before (CONTROL) and 4 min after tolazoline (PRISCOLINE), from J. J., a 14-month-old infant with ventricular septal defect and pulmonary hypertension. At the arrow, pressure was switched from femoral to pulmonary artery. (Reproduced with permission from reference 19.)
appropriate to discuss purpose in scientific papers might take heart from his original article:

> It is required . . . that the blood becomes distributed to the different parts of the lung in such a way, that the alveolar air will give off oxygen and take up carbon dioxide fairly evenly throughout the lungs. . . . If the blood flow becomes inadequate in relation to the ventilation in some parts of the lungs, the corresponding alveolar air will become richer in oxygen and poorer in carbon dioxide than the rest of the lungs. But this will lead to a dilatation of the blood vessels in that part of the lung with a redistribution of the blood as a consequence. It is interesting to note that oxygen want and carbon dioxide accumulation have exactly the reverse local effects on the vessels of the systemic and pulmonary circulations respectively; in both cases, however, they seem to be adapted for their special purposes.

As appealing as von Euler's suggestion might be, local matching of ventilation to perfusion within the air-breathing lung does not explain the function of hypoxia in the fetal lung. There a somewhat different function must be served, because intrapulmonary ventilation-perfusion relationships are irrelevant to gas exchange.
when the lung is filled with fluid. Rather, it seems that pulmonary vasoconstriction in the fetal lung is a part of a bodywide strategy to maintain flow to the placenta, the fetal organ of oxygenation. As is now clear, hypoxic pulmonary vasoconstriction is well developed in the fetal lung.\(^6,7,10\) The greater pulmonary vasoconstrictor responses in young animals compared to older animals\(^8,22\) suggested "that the relatively weak hypoxic pulmonary pressor response seen in the adult mammal may be a remnant of a mechanism which existed in utero."\(^29\) If so, it is important to consider the control of the fetal lung circulation.

Two classical series of studies relating to the lung circulation of fetal sheep had been done at the Nuffield Institute of Medical Research in Oxford, England. The institute was housed in a building designed as an astronomical observatory by Wyatt and Keene, two famous eighteenth-century architects who based their design on the Temple of the Winds at Athens (Fig. 4). With the introduction of gas lighting in an adjacent street, the telescopes were moved to South Africa. Supported by a generous grant from Lord Nuffield in the twentieth century, the building came to house the Nuffield Institute and be used for medical research. There, with collaboration between Oxford and Cambridge scientists, the foundation was laid for our modern understanding of the fetal circulation.

Since the late 1920s, Barcroft at Cambridge had sought to establish the true course of fetal blood flow, attempting thereby to bring order to the unbelievable welter of preexisting theories. Relative to the lung circulation, it was necessary to confirm that the two ventricles in utero really were "a double nut," "with the same office to perform," and were therefore pumping blood in parallel. Historical
Barclay was a radiologist who was retired but was interested in the technology of X-ray cinematography for a variety of purposes. He joined up with Dr. K. J. Franklin, a fellow of Oriel College and tutor in Physiology who had moved with Professor Gunn (my predecessor) from the Department of Pharmacology to apply this new technology in the study of the venous circulation. The story that I was told was that Barcroft had an engagement in Oxford and happened to travel down from London in the same compartment of the train as K. J. Franklin after Franklin had just given an illustrated communication of the application of X-ray cinematography to the study of the venous system of experimental animals and it was, of course, Barcroft's idea to apply this technique to the fetal lamb.

Possibly, the first cardiac cinematography ever performed was done to examine the fetal circulation in the lamb. The result was that superior caval blood was seen to flow primarily into the right ventricle, the pulmonary artery, and through the ductus to the descending aorta (Fig. 5). The inferior caval blood was seen to flow primarily into the left atrium, left ventricle, and out the ascending aorta (Figs. 6A and 6B). Because the two ventricles both pumped blood directly into the aorta, they

**Figure 5.** One frame from a series of rapid-sequence radiographs following injection of radiopaque contrast into the superior vena cava of a mature fetal lamb with an intact umbilical circulation. On the left is a reproduction of the actual radiograph. On the right is the author's interpretation of the path of the contrast from the superior vena cava, through the right heart, resulting in nearly simultaneously filling of the pulmonary arteries and the descending aorta. The path from the pulmonary artery to the descending aorta, not shown in this radiograph, was demonstrated in other studies. Note absence of opacification of the ascending aorta and the arteries supplying the head. (Reproduced with permission from reference 3.)
could be considered to be in parallel and to develop similar pressures, consistent with Harvey's views.

However, these superb radiographs of functional anatomy did not reveal the pressures in the ventricles, the magnitude of pulmonary blood flow, or the changes in pressures and flows at birth. Direct measurements of pressure and flow were required, and Oxford's Temple of the Winds was again the setting for groundbreaking medical research. In 1948, Geoffrey Dawes (Fig. 7) became director of the Nuffield Institute. He developed into a high art the study of the living, exteriorized fetus. His measurements in lambs showed that fetal pulmonary arterial pressure was as high, or higher, than that in the fetal aorta (Fig. 8), confirming the similarity of the pressures in the two great arteries. Pulmonary arterial pressure fell on ventilating the lung with air, but the aortic pressure did not, indicating relative pulmonary hypertension in the fetus. Occlusion of the ductus caused pulmonary arterial pressure to fall further, while aortic pressure rose (Fig. 8), demonstrating that blood now flowed from aorta to pulmonary artery. These concepts have been repeatedly confirmed in laboratories around the world using sophisticated in vivo recording techniques. Thus, within the space of a few years, measurements in Dawes's laboratory had cleared the fog of uncertainty that for centuries had clouded the fetal circulation.

A further series of experiments, done with impeccable measurements of pressure and flow, showed the several factors that contributed to the high fetal resistance and its decrease at birth. Gaseous inflation of the lung, the decrease in alveolar carbon dioxide and the increase in alveolar oxygen all occur with the first breath, and all were found to play a role in decreasing resistance to blood flow (Fig. 9). In addition, in the fetus, high sympathetic tone contributed to the high pulmonary vascular resistance. Hypoxia increased pulmonary arterial pressure in the
isolated, perfused fetal lung, indicating the pressor response was inherent within the lung itself. While mechanical (a collapsed and fluid-filled lung) and neural (high sympathetic tone) factors contributed to the high vascular resistance in the fetal lung, chemical factors (high carbon dioxide, low oxygen) were clearly important. Multiple mechanisms often operate to preserve a vital function, as, for example, in maintenance of systemic arterial pressure in the adult. In the fetus, the normally low fetal oxygen tension, assisted by other factors, maintains high pulmonary arterial pressure and resistance in the collapsed, water-filled lung.

The high lung vascular resistance, in turn, may be important for the maintenance of fetal oxygenation. If the low fetal oxygen levels maintain constriction in certain vascular beds such as the lung, blood flow is directed toward the relatively passive placental bed, which is not constricted by hypoxia. The distribution of blood flow is not only important for normal development of the fetus, but may also become essential in times of hypoxic stress, because cardiac output in the fetus is relatively fixed and placental flow is determined by arterial pressure. To raise pressure, redistribution of flow away from less essential organs must occur. Thus, hypoxia markedly constricts the femoral arterial bed, and the effect is abolished by denervation of the aortic chemoreceptors (Fig. 10). Apparently during the latter part of gestation the maintenance of high resis-

**Figure 7.** Photograph of Professor G. S. Dawes taken in 1968 during an experiment on the fetal lamb in his Nuffield Institute laboratory in the Oxford Temple of the Winds.

**Figure 8.** Schematic pulmonary arterial, femoral arterial, and left atrial pressures, top, and left pulmonary arterial flow, bottom, in the exteriorized mature fetus with an intact placental circulation. Before the onset of ventilation, mean pulmonary arterial pressure is slightly higher than that in the femoral artery, and left pulmonary arterial flow is low. Following the onset of ventilation, pulmonary arterial pressure falls, but not that in the femoral artery or left atrium. Pulmonary flow rises. Occlusion of the ductus arteriosus is accompanied by a sharp rise in femoral arterial pressure and falls in pulmonary arterial and left atrial pressure and in pulmonary arterial flow. (Reproduced with permission from reference 10.)
In 1967 and 1968, I had the opportunity to work on some of these studies, with Dawes, in the Nuffield Institute, then housed in the Temple of the Winds.

It is possible that the hypoxic vasoconstriction of the lung arteries evolved primarily as a mechanism for fetal survival. If so, a powerful mechanism in the fetus might persist after birth and be stronger in the newborn period than in the adult. Our findings in the young calf suggested that such might be the case (Fig. 11). Perhaps the hypoxia of Colorado's altitude constricted the lung arteries in our young patients with ventricular septal defect. Such constriction could be relieved by a vasodilating drug.

The unique features of the lung circu-

tance in the femoral arterial bed depends on hypoxia-mediated activity from the aortic and, to a lesser extent, carotid chemoreceptors. Hypoxia acts directly to constrict flow to the lung and acts via the nervous system to constrict flow to the lower body. In both instances the net result is increased arterial pressure, which should increase flow to the placenta and facilitate oxygen transport to the fetus. Therefore, in the fetus,

"as in the adult, blood flow is redistributed to maintain the circulation through the heart, brain and organs of gas exchange at the expense of blood supply to those tissues which are, in the short term, more expendable."
lation around the time of birth are underscored by the occasionally turbulent transition from fetal life to air breathing. At birth, the lungs must expand with air, the lung arteries must relax for pulmonary arterial pressure to fall, the blood must flow to well-oxygenated alveoli, and all of this must occur within minutes. In approximately 1 of 1,500 live human births, the transition is faulty and neonatal pulmonary hypertension results. The cause is unknown, but precipitating factors often considered are high pulmonary vascular resistance in utero (premature ductal constriction), asphyxia or meconium aspiration during birth, or noxious stimuli in the newborn period (hypoxia, infection). For those newborns not responding to tracheal intubation and hyperventilation with high oxygen mixtures, treatment involves expensive, risky heart-lung bypass for several days. Even so, mortality approaches 20%.

In the early 1980s Kurt Stenmark, a pediatric pulmonary critical care specialist, asked us if we could develop an animal model of severe pulmonary hypertension in the newborn period. He wished to replicate certain features of the human disease, including pulmonary arterial pressure at or above systemic arterial levels, right to left intracardiac shunting, and severe hypoxemia. Also, the small pulmonary arteries should show remarkably thickened walls, particularly with adventitial proliferation, because such vessels are found in infants dying with neonatal pulmonary hypertension (Fig. 12A). The newborn’s capacity to develop pulmonary hypertension, combined with the potential for rapid tissue growth, could produce life-threatening lung vessel thickening. We wondered whether severe hypoxia in the newborn calf could induce similar findings. The newborn calf was a convenient size for study, and previous work at Colorado State University in Fort Collins had indicated that the bovine species seemed susceptible to hypoxic pulmonary hypertension, particularly when compared to other species.

We had experience extending back many years with brisket disease of cattle, which is caused by pulmonary hypertension at high altitude. In the 1950s, Pierson and Jensen with Alexander and Will had reactivated the study of brisket disease at Colorado State University. In 1958 Grover and I joined forces with these scientists at Colorado State University in collaborative research that continues to this day. The first fruit of the collaboration was to show that cattle brought from Kansas to 10,000 feet in South Park, Colorado, developed severe pulmonary hypertension over a period of several months compared to low-altitude cattle. Two years later Bob Grover and I, with the help from his wife Estelle, constructed a corral (Fig. 13) and set it up at 12,700 feet on the summit flats of Mt. Evans, Colorado, for the study of cattle and sheep. Don Will joined us for that experiment, and my
wife, Carol, did the cooking for the research crew. Our infant daughter, Catherine, first learned to stand on Mt. Evans during our time there. Hard physical labor, intellectual activity, and collegial collaboration—all while having one’s family around—must be one of the most satisfying combinations human beings can experience. And so it was for me in that summer of 1960 on Mt. Evans.
A result of that research was that the magnitude of the pulmonary hypertension and the rate at which it developed was greater than what we had observed two years earlier at 10,000 ft in steers of the same age. Thus, the greater the stimulus, the greater the response. Later my study of newborn calves placed in an altitude chamber at 11,000 ft showed even more rapid development of pulmonary hypertension, indicating the important contribution of young postnatal age to the response.

To create an animal model that replicated some of the features of human neonatal pulmonary hypertension, it seemed appropriate to extend our previous experience. Therefore, to accelerate further the development of pulmonary hypertension, we placed newborn calves at even higher altitudes, of 14,000 to 14,500 ft. When we combined the results from all of these studies, it was clear that the rate and severity of the pulmonary hypertension increased with the severity of the hypoxia and with the youth of the cattle (Fig. 14). In particular, putting the day-old calf for 2 weeks at 4,300 to 4,500 m, as reported by Kurt Stenmark and Chris Orton, resulted in suprasystemic pulmonary hypertension, right to left shunting through the foramen ovale and the ductus arteriosus, poor responses to vasodilators, and extreme thickness of the walls of small pul-

Figure 13. Robert F. Grover and his wife Estelle in 1960 at the corral that was set up at 12,700 feet on Mount Evans to study the effect of altitude on cattle and sheep.

Figure 14. Mean pulmonary arterial pressures over time in cattle exposed to actual or simulated altitude. Pulmonary hypertension in yearling steers develops at a slower rate and with a lesser magnitude at 10,000 ft than at 12,700 ft. Newborn male calves more rapidly develop more severe pulmonary hypertension at 11,000 ft than do yearling steers. The most severe and most rapid pulmonary hypertension was seen in newborns at 14,000 ft.
monary arteries (Figs. 12B and C). Such findings resembled those in infants dying of neonatal pulmonary hypertension, suggesting that the newborn calf might be a good model for some aspects of the disease in humans.

Through this model, new insights have been gained into vascular wall biology, particularly by Kurt Stenmark, Norbert Voelkel, and our collaborators, which include the investigative team headed by Bob Mecham at Washington University in St. Louis. Primary questions relate to the relative roles of hypoxia and elevated pressure in producing the vascular abnormalities in the calves and to the cells initiating the changes. The answers are sought in vivo, in vitro, and in isolated cellular systems. In vivo studies utilizing coarctation of pulmonary arterial branches in calves at high altitude suggest that the lower arterial pressure distal to the coarctation is associated with less vascular wall thickening. Also, pulmonary veins, which are hypoxic but have normal intraluminal pressures, remain normal. Culture of whole vessel rings under stretched and nonstretched conditions indicates greater mitotic activity in the stretched vessels. Although such studies do not rule out a role for hypoxia, they do emphasize that pressure per se plays a crucial role in the vascular changes accompanying neonatal pulmonary hypertension.

Although we do not know which cells initiate the wall thickening, we have been surprised at the activation of the adventitia in the hypertensive calves. Such activation occurs early and is of large magnitude. Using bromo-deoxy-uridine, Chris Orton has found greatly increased numbers of adventitial fibroblasts undergoing cell division in the hypertensive calves relative to the numbers of smooth muscle cells. In situ hybridization for RNA of matrix proteins, such as collagen I and fibronectin, also indicate much greater secretion from adventitial cells than from the media in the fetus and in the hypertensive calves. Although there is intense activity in the adventitia, the media is not quiescent in hypertension. For example, in hypertension the normal regression of elastin gene expression is not confined to the inner third of the media but, rather, reverts to the fetal pattern that shows expression across the full thickness of the intralobar arterial wall. By combining physiological techniques with the cellular and molecular biological tools available today, insights not dreamed of a few decades ago may be gained into pulmonary circulatory control under normal and abnormal conditions.

The discoveries appear to proceed at an ever-increasing rate. Looking back over the long reach of history, if I can see more distant horizons, it is because “Dwarfs on the shoulders of giants see further than the giants themselves.” The early Greek and Roman philosophers did the best they could with the tool they had at hand, namely, morbid anatomy. The great advance by Harvey combined a receptive mind with observations in the living ani-

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**Figure 15.** The evolution of understanding in neonatal pulmonary hypertension proceeds at an ever-increasing pace with the utilization of new techniques from different scientific disciplines.
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The modern era was ushered in by physiologists—von Euler, Barcroft, Barclay, and Dawes. Today we have available sophisticated tools of pathology, morphometric histology, cellular and molecular biology and a host of talented investigators who communicate constantly with each other. Each period in history has kept the best of the preceding period while adding advances of its own (Fig. 15). The understanding in the neonatal pulmonary circulation will grow at an ever-increasing rate as long as scientists continue collaborating within and across institutions, within and across disciplines, and within and across the centuries.

Acknowledgments: For the quote, I am indebted to S. Marsh Tenney, who wrote, "The widely quoted, . . . 'on the shoulders of giants . . .' is most often attributed to Robert Burton, but it seems to have originated with Stella Didachus (16th C.)." Pygmaeos gigantum humeri s impositos plusquam ipsos gigantes videre. (Dwarfs on the shoulders of giants see farther than the giants themselves.) I think that this catchy observation has been repeated in various modified forms by many writers . . .—Marsh

References

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