It is fitting and proper for us to continually mention and honor significant contributors to the advancement of knowledge. In so doing the lives and experiences of our great men continue to stimulate the living. As Osler said: "There is a younger generation, too, the members of which are never the worse for the repetition of a good story, stale though it may be in all its aspects to their elders: and then there is that larger audience to be considered to which the season is never inappropriate to speak a word."

Such is the occasion as we address ourselves to the important events in the development of perinatal medicine. William Harvey's singular contributions stand as landmarks or beacons for us today. Across the centuries, his observations and his gift of the experimental approach to the solution of problems facing us in the practice of medicine still stand as the basis for that practice and as a model for the continuous acquisition and evaluation of new information. The purpose of this chapter is to acquaint the reader with the impact of William Harvey's contributions to perinatal medicine through representative examples from translations of his own work. (Figure 1.)

First it is necessary to mention some important events in the life of Britain's most brilliant and honored physician who reintroduced the experimental method in anatomy and physiology and described the circulation of the blood. William Harvey was born on April 1, 1578, in Folkestone, England, the eldest of nine children, to prosperous merchant parents. He attended primary school at King's School in nearby Canterbury. He was educated at Gonville and Caius College, Cambridge, where he received his bachelor
of arts degree in 1957. Because of his academic background, family status, and friends, he attended the University of Padua, Italy, then accepted as the primary medical center of the world, where Galileo's discoveries about the universe were receiving recognition and Harvey's master anatomist teacher, Fabricus de Aquapendente, became his "informant of the way." Harvey was a counselor for the English students there and an honor student and completed his medical degree in 1602. Upon his return to England, he received an M.D. degree from Cambridge. He practiced medicine in London for several years prior to marrying Elizabeth Brown, daughter of the royal physician to Queen Elizabeth and James I, in 1604. In 1607, he was elected to the Royal College of Physicians, a major lifetime interest and an organization in which he held many offices and which became a major recipient in his will. His major hospital appointment was at Saint Bartholomew's Hospital (1609-1643) where he became professor of anatomy and surgery and the Lumleian Lecturer. His royal appointments, first as personal physician to James I, and then to Charles I, no doubt afforded him the financial support and time to complete for posterity De Motu Cordis in 1628, and De Generatione Animalium in 1651. Much of his scientific efforts were not only hampered, but were destroyed during the English Civil War. His death came on June 3, 1657, following a stroke.[2]

In De Motu Cordis, Chapter 6, Harvey clearly differentiates the fetal from adult circulation.

". . . In the foetus the four vessels belonging to the heart, viz., the vena cava, the vena arteriosa or pulmonary artery, the arteria venalis or pulmonary vein, and the arteria magna or aorta, are all connected otherwise than in the adult . . . this membrane in the adult blocking up the foramen, and adhering on all sides, finally closed it up, and almost obliterates every trace of it . . . In the foetus . . . it permits a ready access to the lungs and heart, yielding a passage to the blood which is streaming from the cava, and hindering the tide at the same time from flowing back into the vein. All things, in short, permit us to believe that in the embryo the blood must constantly pass by this foramen from the vena cava into the arteria venosa, or pulmonary vein, and from thence into the left auricle of the heart; and having once entered there, it can never regurgitate.

"Another union is that by the vena arteriosa, or pulmonary artery, and is effected when that vessel divides into two branches after its escape from the right ventricle of the heart. It is as if to the two trunks already mentioned a third were superadded, a kind of arterial canal, carried obliquely from the vena arteriosa, or pulmonary artery, to perforate and terminate in the arteria magna or aorta. In the embryo, consequently, there are, as it were, two aortas, or two roots of the arteria magna, springing from the heart. This canalis arteriosus shrinks gradually after birth, and is at length and finally almost entirely withered and removed, like the umbilical vessels.

"The canalis arteriosus contains no membrane or valve to direct or impede the flow of the blood in this or that direction: for at the root of the vena arteriosa, or pulmonary artery, of which the canalis arteriosus is the continuation in the foetus, there are three sigmoid or semilunar valves, which open from within outwards, and oppose no obstacle to the blood flowing in this direction or from the right ventricle into the pulmonary artery and aorta;
but they prevent all regurgitation from the aorta or pulmonic vessels back upon the right ventricle: closing with perfect accuracy, they oppose an effectual obstacle to everything of the kind in the embryo. So that there is also reason to believe that when the heart contracts the blood is regularly propelled by the canal or passage indicated from the right ventricle into the aorta.

"What is commonly said in regard to these two great communications, to wit, that they exist for the nutrition of the lungs, is both improbable and inconsistent; seeing that in the adult they are closed up, abolished, and consolidated, although the lungs, by reason of their heat and motion, must then be presumed to require a larger supply of nourishment. . . . But we further observe that the passages in question are not only pervious up to the period of birth in man, as well as in other animals, as anatomists in general have described them, but for several months subsequently, in some indeed for years, not to say for the whole course of life, as, for example, in the goose, snipe, and various birds and many of the smaller animals . . . the heart by its motion propels the blood by obvious and open passages from the vena cava into the aorta through both the ventricles; the right one receiving the blood from the auricle, and propelling it by the vena arteriosa, or pulmonary artery, and its continuation, named the ductus arteriosus, into the aorta; the left, in like manner, charged by the contraction of its auricle, which has received its supply through the foramen role from the vena cava, contracting, and projecting the blood through the root of the aorta into the trunk of that vessel.

"In embryos, consequently, whilst the lungs are yet in a state of inaction, performing no function, subject to no motion any more than if they had not been present, nature uses the two ventricles of the heart as if they formed but one, for the transmission of the blood. The condition of the embryos of those animals which have lungs, whilst these organs are yet in obeyance and not employed, is the same as that of those animals which have no lungs . . . (for nature always does that which is best) that she should close up the various open routes which she had formerly made use of in the embryo and foetus, and still uses in all other animals; not only opening up no new apparent channels for the passage of the blood, therefore, but even entirely shutting up those which formerly existed." [3]

From his own words we have not only heard the description of the normal fetal circulation which Harvey clearly differentiated from that of adults, but also of the persistence and shrinking of the ductus arteriosus in humans and animals and his philosophy of nature. Major areas of concern and research in perinatology today are still related to the foetal circulation, specifically with persistent fetal circulation and management of the ductus arteriosus. I shall proceed in discussing Harvey by using a favorite teaching aid (Figure 2) in mentioning some of his contributions to each area. Harvey was interested in respiration and knew that air was breathed. An observation which is of importance to perinatal pathology today is taken from Exercise 70 of De Geneatione Animalium. "The colour of the lungs is deeper than it is in those foetuses that have breathed, because the lungs, dilated by the act of respiration, assume a whiter tint. And by this indication is it known whether a mother has brought forth a living or
Harvey's inquisitive mind was applied to many aspects of the blood including appearance, function, volume and relation to psychological and environmental influences. He attempted to determine blood volume by actual experimentation in animals after assuming adult humans had one and a half to three ounces projected with each contraction of the ventricle. "In the same way, in the sheep or dog, say that but a single scruple of blood passes with each stroke of the heart, in one half hour we should have one thousand scruples, or about three pounds and a half of blood injected into the aorta; but the body of neither animal contains above four pounds of blood, a fact which I have myself ascertained in the case of the sheep."[3] His use of ligatures in description of arterial and venous obstruction and the consequences thereof are classical and each of us who cares for sick newborns utilizes or observes them daily. Influences upon blood flow he states, "Meantime this I know, and would here proclaim to all that blood is transfused at one time in larger, at another, smaller quantities and that the circuit of the blood is accomplished now more rapidly, now more slowly, according to the temperament, age, etc. of the individual, to external and internal circumstances, to naturals and non-naturals-sleep, rest, food, exercise, affection of the mind, and the like.[3]"

In expressing his observations and beliefs of intra and extra uterine nutrition and metabolism, Harvey again has lighted our way and understanding. "And as in the pregnant woman the uterine vessels are relatively larger and more numerous than in any other part of the body, this is likewise the case in the pregnant hind and doe. The arteries, however, contrary to the arrangement in other parts of the body, are much more numerous than the veins; and air blown into them makes its way into the neighboring veins although the arteries cannot be inflated in their turn by blowing into the veins. This fact . . . proves that whilst there is a passage from the arteries into the veins, there is none backwards from the veins into the arteries. The arteries are more numerous than the veins because a large supply of nourishment being required for the foetus."[4] Today we can still use the technique of blowing air into a placental artery to demonstrate a common circulation in the parabiotic syndrome of identical twins whether or not there is a great discrepancy in hemoglobin or size of the donor versus recipient twin. Harvey determined placental anatomy and function as far as the normal eye could perceive. "The placenta . . . presented itself to my eye as a fleshy or fungous excrescence of the womb, so firmly was its gibbous portion connected all around with the uterine walls, which had now grown to greater thickness. The branches of the umbilical vessels struck into the placenta like roots of a tree into the ground."[4] He observed the umbilical vessels, that they do not imbibe any blood from them but that they end and are obliterated in that mucilaginous matter and from it take up nourishment."[4]
The purpose and function of the amniotic fluid were fascinating to Harvey and his observations and interpretations differed from the ancients, in that he believed the amniotic fluid to have a nutritive and protective role rather than to merely represent fetal urine and excrement. Harvey said of the amniotic fluid, "Like the colliquament in the hen's egg, it is a fluid destined by nature for the nourishment of the foetus."[4] He had come to this conclusion by the amount, appearance, taste, and similarity with eggs.

Harvey also felt that the fetus sucks, by what he observed. "Wherefore should we doubt, then that the foetus in utero sucks and that chylopoiesis goes on in its stomach . . . In the stomach there was some chyle not being very different in character from the fluid in which the embryo swam. It also contained some white curdled matter not unlike the mucous sordes which the nurse washes, particularly from between the folds of the skin of newborn infants. In the upper part of the intestines there was a small quantity of excrementuous or chylous matter; the lower bowels contained meconium. . . . In the urinary bladder there was urine, and in the gall bladder bile. "[4] Harvey felt that digestion was ongoing in utero after the fourth month of gestation. In his observations with venesection he observed, "If you take away some blood shortly after a meal, before the second digestion has been completed and the serum has had time to descend by the kidneys, or at the commencement of an attack of intermittent fever, you will find it sanious, inconcoct, and abounding in serum. On the contrary, if you open a vein after fasting, or a copious discharge of urine or sweat, you will find the blood thick, as if without serum, and almost wholly condensed into clot." [4] Harvey favored breast feeding for most women and had a philosophy of introduction of other foods. "Just as the young of the viviparous animal lives upon milk from the mammae of its mother, until it is provided with teeth by which it can masticate harder food. . . . For as the foetus acquires greater powers of digesting, so is it supplied with food that is successively thicker and harder." [4] He cautions against the use of wet nurses during teething, "For mercenary nurses being for the major part of more robust and hardy frames, and their milk consequently thicker, more caseous, and difficult to digestion, it frequently happens that milk of this kind given to infants . . . during the time of teething, is not well borne, but gives rise to crudities and diarrhoeas, to griping, vomiting, fever, epilepsy, and other formidable diseases of the like nature.[4]

Over the past quarter century, I have also had much interest in the size, appearance of wasting, degree of maturation and wasting of infants of varying gestational ages as incorporated into the often used Figure 3. Comments and observations of Harvey were stimuli for my investigations upon the small for gestational age infants, the parabiotic syndrome, amniotic fluid studies, and other ventures into the physiology and metabolism of the newborn. Surely Davison and Bruton are my moderns and informants of the way and Harvey my ancient leader. Even in his study of chick embryos, Harvey reported, "Some are found more precocious and forward, having everything more precocious and formal, having everything more distinct; others, again, are more sluggish and these have the parts less apparent," [4] for date. In his treatise on Parturition he states, "Some nine month's children are very small, much less in fact than many foetuses of eight months, nevertheless they do not abide longer in the womb. And as to weight, any twins of eight months are far heavier than a single nine months' child; yet they are not expelled before nine months are completed."[6] In the treatise on Humours, "And so some women are seen with the abdomen immediately distended, and yet they bring forth a little shrivelled foetus accompanied by a vast flow of water."[7] A statement of Harvey's which applies to nutrition and blood
flow is, "In like manner, that which is abundantly nourished increases; what is not sufficiently supplied shrinks; what is perfectly nourished preserves its health; what is not perfectly nourished falls into disease. The blood, therefore, even as the soul, is to be regarded as the cause and author of youth and old age, of sleep and waking, and also of respiratory; all the more and especially as the first instrument in natural things containing the internal moving cause within itself. "[4]

Although physicians of Harvey's time were not aware of the specific causes of infections, they had ascertained routes for contagion and specific responses within the host. In proof of his circulation of the blood Harvey used these examples relating to infection, "The phenomena alluded to are those that present themselves in connection with contagions, poisoned wounds, the bites of serpents and rabid animals, lues nevera and the like. We sometimes see the whole system contaminated, though the part first infected remains sound. . . . When it appears that the contagion impressed upon or deposited in a particular part, is by and by carried by the returning current of blood to the heart, and by that organ is sent to contaminate the whole body. . . . In local inflammations, where, so long as the swelling is on the increase, and has not reached its extreme term, a full pulse is felt in the part, especially when the disease is of the more acute kind, and the swelling usually takes place most rapidly."[3]

Harvey's interest in development and epigenesis, led him to study not only animals, but any human material available to him and thus on to some teratological observations. He noted malformed products of conception from the first trimester and called them disorders of conception. "Such a discharge is particularly observed among women when they miscarry in the course of the first or second month. I have repeatedly seen such ova aborted at this time; and such was the one which Hippocrates has described as having been thrown off by the female pipe-player in consequence of a fall."[4] Harvey mentions the presence of cleft lip in animals and humans, "the oral aperature without lips or cheeks is seen stretching from ear to ear; and this is the reason, unless I much mistake, why so many are born with the upper lip divided as it is in the hare and camel, whence the common name of harelip for the deformity. In the development of the human foetus the upper lip only coalesces in the middle line at a very late period. [4] In another abortus or form of anencephaly he found, "the brain itself was of the consistence of curdled milk. Instead of a cranium there was a coriaceous membrane, in some places cartilaginous, and divided down the forehead to the roots of the nostrils."[4] In another embryo he described what appears as adrenogenital syndrome, "the pudendum was like that of the rabbit, the labia standing for prepuce, the nymphae for glans. In the upper part the root of the penis was also apparent, and on either side for the testicle there was the lax skin of the scrotum. The uterus was extremely diminutive, and in figure like that of the ewe or mole, with two horns. And as the prostate glands are situated near the penis of the boy, so were the testes (ovaries) of visible dimensions, seen adjacent to these cornua. Externally considered, the sex seemed that of the male; internally, however, it was rather that of the female."[4] Different notations of heart findings were made of abnormalities in Prelectiones. [5]

Harvey was familiar with iatrogenesis and mentioned it in regard to midwives, "Hence it is that midwives are so much to blame, especially the younger and more meddlesome ones . . . daubing their hands with oil, and distending the passages, so as not to appear ignorant in their art-giving besides
medicines to excite the expulsive powers, and when they would hurry the labour, retarding it and making it unnatural, by leaving behind portions of the membranes, or even the placenta itself, besides exposing the wretched woman to the air, wearying her out on the labour stool, and making her, in fact, run great risks of her life. "[6]

Harvey had warned us of the routes of absorption of specific drugs of his day and the peculiarities of the newborn's skin. Would that we had listened prior to the widespread use of antibiotics, antiseptics (hexachlorophene), steroids, etc. He stated, "the skin may be regarded as the principle means of defense or protection and is well devised by nature, who, indeed, never does aught amiss, that these parts are the last to be engendered, inasmuch as they could never be of use or avail as defenses until the animal was born."[3] I feel he meant fully developed term infants. In regard to drugs he said, "When we perceive, further, that medicines applied externally exert their influences on the body just as if they had been taken internally, the truth we are contending is confirmed. Colocynth and aloes move the belly, cantharides excite the urine, garlic applied to the soles of the feet assists expectoration, cordials strengthen, and a infinite number of examples of the same kind might be cited."[3]

Harvey made few comments about the central nervous system of the foetus save for development, "The head is therefore very large at first, in comparison with the rest of the body, which it far surpasses because of the brain and the eyes, and the larger quantity of moisture contained in them. These parts, nevertheless, are among the last to be perfected, for the brain acquires consistency with difficulty, and it is long before it is freed from cold and moisture in any animal, and especially in man. The sinciput, too, is consolidated the last, the bones here being quite soft when the infant sees the light."[4] He also observed hydrocephalus and its consequences.[5]

History is grateful to George Gent for collating and publishing De Generatione Animalium. Although Harvey's explanations and conclusions on fertilization were later proven incorrect following use of the microscope, his descriptions of what he could see after the eighth week of gestation and the functions he attributed to the organs as they developed have mostly stood the test of time and many have already been mentioned.[2]

That Harvey was interested in the practice of obstetrics is confirmed in most of his writings. He was a diagnostician, an innovator of equipment and techniques, and had sufficient experience to offer prognosis. Examples to illustrate these points are to follow:

"So women in robust health usually experience easy and rapid labours; the contrary holding good in those whose constitutions are shattered by disease. . . . Nature in her provident care, contrives this dilatation of the parts in order that the foetus may come into the world like the ripe fruit of a tree."[6] This was the first historical notation of the relaxation of the pelvic bones. As to the time of labor he said, "It is probable the foetus seeks its exit on account of deficiency of nutriment,"[7] and "In other animals there is one fixed time, but in man several; for the human foetus is expelled both in the seventh and tenth months, and at any period of pregnancy between these; moreover, when the birth takes place in the eighth month, it is possibile for the infant to live."[6] Today infants can live at about 25 to 26 weeks
Historical Review and Recent Advances - Chapter 26

gestation due to progress in neonatal care. "If the foetus is diseased or feeble, or is born before full
term . . . for some days after birth it neither properly takes the breast nor gets rid of its excretions . . .
These then, are the circumstances which immediately precede birth; and then it happens that the
presence of milk has been regarded as a sign of approaching delivery . . . it is therefore never observed
before the seventh month of pregnancy . . . In difficult labours it often happens that the foetus is
retained in the passages many hours without the possiblity of breathing yet is found to be alive; when,
however, it is once born and has breathed, if you deprive it of air, it dies at once. In like manner children
have been removed alive from the uterus by the Caesarean section many hours after the death of the
mother.[6]

Harvey obviously was in attendance at complicated deliveries, from this observation, "Besides in a
tedious labour we learn whether the infant is alive or not by the pulsation of the umbilical arteries; and it
is certain that these arteries receive their impulse from the heart of the foetus and not of the mother, for
the rhythm of the two differs: this can be easily ascertained if one hand is applied to the wrist of the
mother and the other to the umbilical cord." 8  His understanding of prematurity and high risk pregnancy
is illustrated with this comment, "Of unnatural labours, therefore, there are chiefly two kinds; either the
foetus is born before the proper time and this constitutes abortion, or else subsequently to it, when a
difficult or tedious labour is the result either from the due time and order not being preserved, or from
the presence of dangerous symptoms.[6]  He understood that all premature rupture of the membranes was
not a bad prognostic sign as he recalls, "I have often seen the waters come away in the middle of
pregnancy, and abortion not take place, the child remaining strong and vigorous until birth."

Harvey appreciated the placenta in regards to fetal outcome as he stated," . . . where parts only of the
product of conception escape, whilst others remain; for instance, if the foetus itself is disposed to come
away when the placenta is not yet separated from the uterus, or on the other hand, if the placenta is
separated when the foetus is not rightly placed or the uterus is not sufficiently relaxed to allow
passage."  [6]

Superfoetation was observed by Harvey as described, "In the case of other women in whom the foetus
has died in the third or fourth month, then putrified, and came away in the form of fetid lochial
discharges, we have known superfoetatio to take place; and yet these same women have persisted that
they have brought forth their children after the completion of the fourteenth month."  [6]

He also mentions pseudocyesis, "it is impossible to deny that many women, either for purpose of gain or
from fear of punishment, have simulated pregnancy, and not hesitated to swear to the truth of their
assertion; others again have frequently been deceived, and fancied themselves pregnant, whilst the
uterus has contained no product of conception."[6]

Puerperal infection was experienced by one of his patients whom he cured as follows: "A noble lady in
childbed being attacked with fever for want of the ordinary lochial discharge, had the pudenda swollen
and hot; finding the uterine orifice hard and firmly closed, I forcibly dilated the part by means of an iron
instrument sufficiently to admit of my introducing a syringe and throwing up an injection; the effect of
which was that grumous and fetid blood, to the amount of several pounds, flowed away, with present relief of the symptoms." [6]

Mrs. Harvey was barren and Harvey was not able to help her, however, the wife of a doctor of divinity did have a cure as he mentions, "I was . . . called to her, I opened the uterine orifice and immediately two spoonfuls of pus came away of a sanious character and tinged with streaks of blood. On seeing this I said that there was a hidden ulcer in the uterine cavity and by applying suitable remedies I restored to her former state of health."[6]

With these examples I hope to have provided some of the spectrum of genius of William Harvey and will again use his words in closing: "Man comes into the world naked and unarmed, as if nature had destined him for a social creature and ordained that he should live under equitable laws and in peace; as if she had desired that he should be guided by reason rather than be driven by force.[4] . . . Nature is no where accustomed more openly to display her secret mysteries than in cases where she shows trace of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease. For it has been found in almost all things that what they contain of useful or applicable, is hardly perceived unless we are deprived of them, or they become deranged in some way. [9] . . . I doubt but that many things still lie hidden in Democritus's well that are destined to be drawn up into the light by the indefatigable diligence of coming ages.[10] . . . Our first duty is to inquire whether the thing be or not, before asking wherefore it is."[3]

For those who will read his work and follow his way, the light of the life of William Harvey continues to stimulate us toward greater understanding and better care of the patients to whom our lives are dedicated, those shortly to be born or those in trouble.

REFERENCES


Fig. 1. Photograph of William Harvey, courtesy of the Malloch Rare Book Room of the New York Academy of Medicine.

Fig. 3. Andrews, B. F.; The Small for Date Infants. *Pediatric Clinics of North America* W. B. Sanders 1970.