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Marc Glickstein
Yale University

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THE USE OF INDOMETHACIN IN TREATMENT OF THE PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS: A REVIEW OF THE LITERATURE AND THE YALE EXPERIENCE

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Marc Glickstein

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TO JUDITH

for her support sustinence and effort
over the past four years

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I. Introduction

In describing the clinical findings associated with the patent ductus arteriosus more than twenty years ago, Burnard[1] wrote.........

> A murmur which possessed certain characteristic properties was heard in.....premature babies... and has been attributed to flow through the ductus arteriosus from aorta to pulmonary artery. In premature babies....there was a clear connection with dyspnea, and the murmur was not heard unless respiratory distress was present. In some prematures the murmur disappeared and then returned if their condition deteriorated...There is good evidence that the ductus arteriosus remains open for twenty-four hours or more after birth in the human baby....The fact that the murmur has only rarely been heard after normal birth suggests that in the situations where it was detected....there was departure from the normal conditions governing flow across the ductus.

Recent years have witnessed a burgeoning body of research that greatly clarifies a number of variables that contribute to the "departure from normal conditions" in the pathophysiology of the patent ductus arteriosus (PDA) in the preterm infant. These include the effects of age and the degree of prematurity, influence of associated lung disease, and the development of congestive heart failure.

The mechanisms for ductal patency and closure in the preterm infant have been intensively studied in the laboratory setting, and have been related to numerous factors, perhaps the most influential of which appears to be prostaglandin activity. Recent advances in prostaglandin research have described the role of these substances in normal and abnormal physiology, and have demonstrated their involvement

in pre- to post-natal changes in the vascular system. This has led to use of indomethacin, a prostaglandin synthetase inhibitor, to intervene pharmacologically and close the patent ductus in those premature infants where a PDA is maintained, and has enabled effective and non-surgical implementation of therapy in this typically compromised group of patients. Prior to this, treatment of a symptomatic patent ductus was mainly supportive, with surgical ligation being performed as a last resort due to high levels of morbidity and mortality in performing an operative procedure on tiny, immature babies who usually weighed less than 1750 grams.

This paper will attempt to review the literature regarding the structure and function, physiology, pharmacology, and treatment of the PDA especially as it relates to the premature infant. Included will be a presentation and discussion of the role of indomethacin in the management of twenty-eight pre-term infants in the Newborn Special Care Unit at Yale-New Haven Hospital over the past two years.

II. Ductal Embryology and Morphology

A. Embryology

The ductus is derived embryologically from the sixth aortic arch, the last in a series of paired vascular structures that develop early in fetal life as branches of the primitive dorsal aorta, and undergo varying degrees of degeneration and transformation. The sixth arch extends branches to the lungs which become the pulmonary arteries, and maintains a vascular segment between the aorta and the left pulmonary artery which represents the ductus.

In the fetus and neonate therefore, the ductus can be seen to originate at the bifurcation of the main pulmonary arteries, and to terminate at the aorta just distal to the origin of the left subclavian artery. This location, as well as its size, which in the fetus may be equal to the aorta, enables it to serve as a conduit between the right heart and the systemic circulation.

B. Morphology

Although the ductus is in direct continuation with the pulmonary artery and the aorta, its structure differs from the adjacent vessels.[2] In cross section there are three distinct layers: a thick media surrounding an internal elastic lamina, within which resides an intimal layer of varying thickness, depending on the gestational age and degree of constriction that has taken place.[3] An adventital layer of loose connective tissue surrounds the entire vessel.[4] It has been shown histologically[5] that the medial wall of the ductus contains greater amounts of mucopolysaccharide ground substance, as well as a

spiral muscular arrangement, not present in either the aorta or the pulmonary vessels. There are only very sparse amounts of elastic fibers present in the media in contrast to the greater amounts found in the aorta and pulmonary arteries. The spiral muscular arrangement enables the ductus to shorten at the same time it is undergoing active constriction after birth. This layer possesses a greater resemblance to the muscular than to the elastic arteries with which it is in direct continuation.

As the gestational age of the fetus increases there is pronounced intimal proliferation which ultimately contributes to its obliteration. The ductus is differentiable histologically from the adjacent aorta and pulmonary artery only at about 12 weeks, at which time the intimal layer is absent. The intimal layer appears at 16 - 17 weeks of age as a very thin layer which continues to duplicate and thicken up to birth. Large cushions are present at about 28 weeks gestation and their growth is accompanied by disruption of the internal elastic lamina.[3] After birth continued proliferation occurs until the cushions oppose each other and obliterate the lumen. At the same time intimal growth occurs in the immediate post natal period, cellular disintegration and necrosis takes place in the media. Nuclei become pyknotic and there is complete loss of cellular architecture in this region. This may be due to anoxia of this portion of the ductus and contributes to functional and anatomic obliteration.[6,7]

The persistent ductus is a congenital morphological abnormality distinct from the patent ductus arteriosus, the physiologically im-

mature and unresponsive entity of the premature. The congenital persistent ductus is distinguished from the patent ductus of the premature in that the former is not associated with prematurity, may have a genetic component, and possesses structural abnormalities in the vessel wall that prevent normal constriction. A constant finding in the persistent ductus is an additional subendothelial elastic lamina adjacent to the lumen and lying on top of the normally exposed intimal layer.[8] This prevents intimal proliferation and closure. It has also been noted[3] that cases of persistent ductus arteriosus also contain relatively more elastic fibers in their media than do control ducti.

III. Role of the Ductus in the Fetal Circulation

A. Fetal Circulation

In the fetus the circulation possesses a parallel rather than a series arrangement. Thus both the right and left ventricles pump blood directly to the systemic circulation instead of the entire burden for delivery of systemic blood flow being one incumbent upon the left ventricle as it is in the adult. This situation is made possible by the ductus arteriosus.

The right ventricle in the fetus accounts for 2/3 of the combined ventricular output and receives return from the superior vena cava, coronary sinus, and about 60% of the return from the inferior vena cava. This blood is ejected by the right ventricle, traverses directly into the ductus and then to the descending aorta and systemic circulation. The left ventricle ejects about 1/3 of the combined ventricular output, most of which goes directly to the systemic circulation.[9]

The fetal lungs are fluid filled structures in utero that receive only about 7% of the combined ventricular output. In the fetus, the placenta serves as the organ of gas exchange and here oxygenated blood with a saturation of about 80% is delivered to the fetus from the mother. Since the lungs in the fetus do not function in gas exchange, cardiac output is not spent in delivery of significant amounts of blood to the pulmonary circulation. Instead, the ductus allows for the majority (<90%) of the right ventricular output to bypass the lungs and be delivered to the systemic circulation.

While more than 60% of combined ventricular output traverses the ductus, only about 7% of total ventricular output is delivered to the lungs. Thus cardiac output is not required for maintenance of pulmonary blood flow and the work performed by the right ventricle is contributed towards maintaining systemic cardiac output instead. This results in a 50% decrease in workload of the heart and appears to be the major function of the ductus in the fetus.[9]

B. Circulatory Changes at Birth

At birth, the pattern of distribution of fetal blood flow is dramatically changed to accomodate the transition from pre- to post-natal life.[10] Several factors including changes in pulmonary and systemic vascular resistance and changes in the path of blood flow contribute to this transition.

First and foremost is a rapid decrease in pulmonary vascular resistance associated with ventilation of the previously unexpanded fetal lungs. Pulmonary vascular resistance actually begins to fall several weeks prior to birth as a result of rapid growth of new vessels producing an increased surface area, but the largest stimulus is by far, that of initial oxygenation of the lungs. Studies in fetal lambs have shown that pulmonary vascular resistance changes from 1.6 to .3 mmHg/ml/min/kg before and after birth, a change of 80%. This decrease in arteriolar resistance in turn, allows a dramatic increase in pulmonary blood flow from a prenatal level of about 35 ml/kg/min to 160-200 ml/kg/min.[11]

Initial ventilation results in an increase in pulmonary alveolar P_A02 which may influence pulmonary vascular smooth muscle to dilate either directly [12] or indirectly. [13] In the latter situation it has been postulated that oxygenation of the lungs may in turn promote release of chemical mediators such as bradykinin into the pulmonary circulation which has a dilatory effect on the vasculature there. This was shown to be accomplished either by mechanical ventilation with oxygen or by exposure of the pregnant ewe to hyperbaric oxygen thereby increasing the fetal pO_2 without any mechanical expansion. The net result is that an increase in pulmonary arterial pO_2 with or without mechanical expansion leads to the release of bradykinin and in turn a decrease in pulmonary vascular resistance.[13,14]

A second major contribution in the transition from fetal to neonatal circulation is the rapid increase in systemic peripheral vascular resistance associated with the cessation of the placenta as an organ of gas exchange, and the removal of its low resistance circulation from the systemic circut.

Finally there is closure of the foramen ovale occurring as a combined result of the previous changes. Left atrial pressure is increased over right atrial pressure secondary to the change in distribution of blood flow. Right atrial pressure is decreased as a result of less inferior vena caval return after removal of the placenta, while left atrial pressure rises following increased pulmonary venous return. These then oppose the foramen ovale against the crista dividens and provide functional closure of this communication.

In those situations where persistent patency of the ductus may occur, the effect of these events on total peripheral resistance is to change the direction of circulatory shunting from the right to left shunt present in utero to a left to right ductal shunt as the left ventricle increases its systemic output by 25%.[11] This reversal of flow through the ductus may result in a continuous murmur and is often heard in normal infants in whom the ductus may not completely close for several hours after birth.[1] In most instances functional closure occurs within 10-15 hours after birth, [9,11] but complete anatomical closure may be delayed up to three weeks as fibrosis, hemorrhage, and total obliteration of the lumen occurs. [5,11]

IV. Physiology and Pharmacology of the Isolated and Intact Ductus

A. Developmental Parameters

The profound growth of the fetus during the gestational period contributes to an age related profile of physiological responsiveness to various stimuli that varies with the developmental level, and contributes to the frequent correspondence of patent ductus arteriosus with prematurity.

Hornblad [15] had demonstrated the insufficiency of ductal smooth muscle in premature fetuses and has shown the relative increase of the muscle layer with age. The decreased constrictor response as a result of this is postulated to account for the lack of closure in this group and it has also been shown that generation of actual tension is positively correlated with gestational age [16] as is the degree of constriction achieved.[17]

The direct stimulation of oxygen in closing the ductus is well known [9] and has been shown to mediate constriction in various isolated animal preparations. Several factors in the premature neonate alter the levels of arteral $PaO2$. While normal term babies reach adult levels of arterial $PaO2$ within 2 days, very premature infants may not ever reach a normal PaO_2. This is a function of the peak arterial PaO_2 which varies directly with the degree of prematurity. [18] The frequent association of patent ductus arteriosus with respiratory distress syndrome (RDS)[19,20] also serves as a source of lowered oxygen tension in the premature. However, McMurphy and others have shown [17,21]

that even with delivery of normal amounts of O_2 to isolated ductal smooth muscle, the overall response of the ductus to O_2 is related to gestational age, with decreasing levels of O_2 being necessary to produce constriction as the gestational age increases.

Prostaglandins have been broadly implicated in ductal function, and it has been hypothesized that developmental variations in their metabolism may have some role in the failure of the ductus to close in preterm infants.[22] Similarly, while administration of the prostaglandin systhetase inhibitor, indomethacin, results in constriction of the ductus, a gestational variation in sensitivity has been noted.[23] Rat fetuses studied with whole body preparation methods are completely unresponsive when less than 18 days gestational age. Twenty day fetuses are 50% as responsive, and 22 day (term) fetuses are fully responsive to its effects.

There is also an age related ductal response to indomethacin in the post-natal period. Those infants treated earlier in life (less than 2 weeks old)[4,24] have a higher rate of ductal closure than those treated later (older than 2 weeks).[25] Several unsuccessful cases have been reported [26,27] of attempts to close a persistent ductus in children of school age, but is important to note that this group, as well as some full term babies who exhibit patent ductus arteriosus, more likely suffer from a congenital structural abnormality in the vessel wall rather than the physiological unresponsiveness present in the premature infant. [24,28,29]

B. Effects of Oxygen

In the lamb the ductus is exposed to a pO_2 of 18-28 torr in utero which rapidly rises to levels of 50 torr or greater soon after birth.[9] It has been shown in both isolated[17,30,31] and intact[32] ductal preparations that increases in the oxygen environment produce constriction of the ductus. Maximum sensitivity to oxygen in the isolated neonatal ductus occurs between a range of 0-100 torr, and little additional constriction is noted past levels of 200 torr, which indicates that ductal responsiveness is confined almost entirely within the range of physiological changes encountered in fetal to neonatal transition.[33] Ductal constriction to oxygen occurs irrespective of mechanical expansion of the lungs as ventilation of lungs with nitrogen alone produces no change in ductal diameter,[11] while placing the mother in a hyperbaric oxygen chamger, thereby increasing the amount of O_2 delivered to the ductus produces constriction[34] while the fetus is still in utero. In the term fetal lamb the initial level of pO_2 necessary to induce ductal response is 50-60 torr.[16]

The minimum increase in the level of O_2 above this baseline necessary to produce ductal constriction in a given fetus is not immediately apparent, as this varies with gestational age. However McMurphy has demonstrated in ducti removed from fetal lambs that the greater the amount of O_2 above the baseline delivered to the ductus, the greater its response, up to values of about 700 torr.[17] Even with high levels, however, the initial response may be slow and take up to 10 minutes to develop, while maximal response can take up to 30 minutes to be achieved.[16]

An intersting result reported by Oberhansli-Weiss demonstrated that decreasing, as well as increase O_2 levels produces constriction of the isolated ductus.[16] Although the levels of tension generated by the low levels of O_2 are not quite as great as those produced by high O_2 levels, they are nevertheless significantly greater than baseline. This same study also showed that sequential exposure of the ductus to first high and then low pO_2 resulted in a constrictor response that approached the maximal tension after each exposure to high or low O_2. The maximal tension developed at high pO_2 after several exposures was not significantly different from that developed from multiple exposures to low pO_2, and this may be a result of permanent changes in the muscle itself.

The evidence is apparent that oxygen is a potent stimulus to ductal closure. This is generally accepted despite the fact that the wealth of evidence is inferred from isolated rather than from intact ducti. Some early investigators argued that oxygen was the sole stimulus to contraction[35] and this was supported by others[31,33] although it is now apparent that there are other factors involved. The mechanisms responsible for oxygen induced constriction are not entirely clear but Fay[33] has suggested that the contraction of the ductus is due to a direct effect of O_2 on the smooth muscle itself.

It has recently been shown that contractile responses to oxygen in in vitro ductal preparations may be modified to a significant degree by ambient light.[36] Room light was shown to relax oxygen induced contractions in immature ducti, but not in mature vessels and the age

related differences in responsiveness to oxygen were abolished when the experiments were conducted in a dark environment. This may have some bearing on isolated studies that have shown age related responsiveness to oxygen stimulation,[17] but still imply biochemical differences in vessels of varying gestational ages.

Specific agents (i.e. sodium cyanate) have been shown to prevent normal ductal responsiveness to oxygen.[33] An interaction between oxygen and the cytochrome enzymes has been proposed since all of the agents tested that do block ductal response to O_2 have in common the property of preventing synthesis of high energy phosphate compounds by inhibiting or uncoupling the respiratory transport chain. Compounds such as xylocaine or tetrodotoxin that simply block local neuronal input do not abolish ductal constriction. Also, treatment of the ductus with carbon monoxide, which is known to bind to cytochrome A_3, prevents oxygen induced contraction.[28] This inhibition may be reversed by illumination with light of specific wave length which is known to dissociate carbon monoxide from the cytochrome enzymes and allow interaction with oxygen to occur. A three step sequence of events is hypothesized to operate in O_2 induced contraction. These are 1) interaction of O_2 with terminal oxidase of the cytochrome chain resulting in 2) increased electron flow along the cytochrome finally producing 3) increased synthesis of high energy phosphate compounds, which in turn triggers muscular contraction. Other investigators have published supporting histochemical evidence demonstrating presence of significant amounts of enzymes involved in oxidative metabolism that suggest that this mechanism plays an important role in the functional changes observed.[37]

C. Autonomic Mechanisms

While the changes observed following exposure of the ductal smooth muscle to oxygen are striking, other mechanisms probably play a significant role in closure. Vasoactive agents have been shown by a number of authors to have marked effects on ductal responsiveness in isolated[9,11,16,17,38,39,40] and intact[41] experiments. Oxygen, in addition to a direct effect on the ductus may have an indirect effect by liberating a stored chemical mediator.[13]

A significant number of adrenergic terminals have been demonstrated in the media of the ductus[2,39,42] which is a quantitatively different finding from the adjacent aorta and pulmonary vessels.

Boreus et al[39] has shown by flourescent histochemistry, rich plexuses of norepinephrine containing nerve terminals in 10-24 week old human fetal ductuses. Although other authors have differed somewhat in the exact location in the media in which the adrenergic terminals have been demonstrated, there appears to be general agreement as to their presence and influence in changes of ductal tone.

Through specific staining techniques it has been shown that there are also terminals containing acetylcholinesterase in the ductus but the distribution of these fibers is different from the adrenergic ones.[38] Cholinesterase staining demonstrated presence of actetylcholinesterase only in scattered bundles which were located in the periphery of the ductus. These fibers only occasionally gave off smaller branches and these did not usually extend into the muscle coat.

Treatment of the ductus with vasoactive agents has been shown to produce a significant variety of responses that vary in both intensity and interaction with other physiological mechanisms. Both epinephrine and norepinephrine have been shown to constrict the ductus, and this is predominately via alpha receptors, as demonstrated by the fact that phenoxybenzamine,[38] and phentolamine,[39] selective αblockers, prevent this effect. The contribution that adrenergic input actually has in the ductal closure in the neonate is somewhat uncertain since the concentrations of epinephrine and norepinephrine used in these isolate studies were at high levels and above those normally found physiologically,[38,39] Also the constrictor responses resulting from prior exposure to oxygen were not modified by α or β blockade, showing at least that the influence of O_2 in constriction overrides that of epinephrine and norepinephrine, and argues that participation of catecholamines in ductual closure is unlikely.[16,31] Furthermore, pretreatment of the ductus with reserpine, which presumably results in depletion of catechols, also does not block its response to oxygen.[43]

The role of Acetylcholine (Ach) in ductal closure seems to be associated with a more definitive physiological role resulting in significant changes in tone over a range of normal biological concentrations. When compared to catecholamines, equimolar physiological concentrations of Ach generate significantly greater changes in flow through the intact ductus.[41] Ach has been shown to produce a dose dependent contractile response in the ductus of the 10-24 week old human fetus[39] and suggests that development of cholinergic receptor function is fully developed at a very early stage in fetal development.[40]

The immature ductus in fetal lambs less than 1/2 term is unresponsive to O_2 but does constrict in response to additon of Ach in a bath containing the isolated ductus. In older lambs who are responsive to changes in $O2$ this response may be blocked by atropine suggesting that increases in O_2 may lead to release of Ach which in turn constricts the ductus. Acetylcholinesterase also produces the same inhibition of the constrictor response to O_2 and addition of edrophonium, and acetylcholinesterase inhibitor, produces subsequent constriction of the ductus. These findings suggest that local Ach plays a role in constriction of the ductus and it is, in turn, coupled in some way to changes in O_2 environment.[11,16] It has been suggested that the effects of Ach are due to a direct constrictor effect.[41]

An interesting result is the observed interaction of Ach with O_2. McMurphy et al[17] has shown that Ach decreases the O_2 induced constrictor threshold in an isolated ductal preparation. In other words, pretreatment of the ductus with Ach decreased the pO_2 at which O_2 induced constriction first occurs. In addition Ach has been shown to increase the degree of constriction attainable with $O2$ alone, and this augmented contractile response is observed at every level in a wide range of oxygen environments tested.

Although a wide variety of other vasoactive agents have been tested, including tyramine, histamine, 5-hydroxytryptamine,[38,40] it is significant to note that Ach produces a greater degree of contraction than any other drug tested. These findings plus those of the interaction and augmentation of Ach with oxygen suggest that Ach is a likely determinant in ductal closure.

Kinins have also been shown to have effect on circulatory changes in the ductus. In the lamb kininogen is present as early as 61 days of fetal life (gestation 140-150 days) and is found in increasing concentration up to term. Formation of bradykinin from kininogen is dependent on oxygenation of the blood and high concentrations of bradykinin begin to appear within 1-2 min after ventilation.[13] While kinins dilate fetal pulmonary vasculature they have been shown to constrict the ductus arteriosus and a contributory role for these agents is also possible.

D. The Effect of Prostaglandins on the Ductus

Prostaglandins (PG) are among the most potent autocoids known and their presence has been demonstrated in nearly every tissue.[33,44] Rapid catabolism by enzymes located in the lung renders about 90-95% of the prostaglandin inactive upon a single passage through the pulmonary vasculature. In the fetus the presence of ductal shunt may enable them to bypass pulmonary degradation and allow them to exert their hormonal effects systemically to a greater extent.[22,45]

The response of the ductus to prostaglandins has been carefully studied. Coceani and Olley[46] have shown in vitro that prostaglandins relaxed the ductal musculature in the lamb and that this effect is best seen in the absence of oxygen. Prostaglandins of all types (A,E,F) produced the same response but PGA and PGF were able to relax the ductus only at much higher concentrations (10^{-6}-10^{-5}m) than PGE (10^{-9}m).

Starling and Elliott [47] confirmed these in vitro observations in the calf with respect to prostaglandins of the E series but obtained discrepant information with regard to PGF. They showed that in the presence of oxygen, $PGF_{2\alpha}$ produced constriction of the ductus and attributed this finding to a specific release of cGMP by PGF. The same

constrictor effect was demonstrated by treatment of the ductus by cGMP alone. PGE results in higher levels of cAMP and dilates the ductus, and it is shown that at low levels of O_2 there is more PGA and PGE. Changes in oxygen level may thus change the relative amounts of the different prostaglandins and it is suggested that changes in the cAMP/cGMP ratio secondary to levels of specific prostaglandins affect ductual tone, such that decreasing the ratio (increasing cGMP) produces ductal constriction.

Other in vitro studies [48] by the same authors confirm the constriction effects of $PGF_{2\alpha}$ and they show that this effect is synergistic with that of oxygen. They do however use higher than physiological levels of $PGF_{2\alpha}$ to achieve their effects. In vivo studies on rats and rabbits [49] have given somewhat different results and have shown that infusion of PGE and PGF both contributed to dilation of the ductus after it had begun to close following partrition. This effect is specific for ductal musculature and no change is shown on the adjacent aorta or pulmonary vasculature.

Animal studies have therefore demonstrated a consistent dilatory action for PGE_1 and PGE_2 but a somewhat equivocal response to PGF . This discrepancy may be the result of a species variability to the effects of specific prostaglandins but may also reflect methodological differences as a function of in vitro vs. in vivo responsiveness to the agent.

With regard to oxygen levels and response to PGs, it is important to note that in most tissues prostaglandins are dependent on O_2 to exert their effects.[50] In the ductus however, maintainence of patency in PGs

requires a lack of O_2 since their ability to relax the ductus[46] and the concentration of PGs producing relaxation[47] are inversely related to O_2 levels. Thus in the low oxygen environment present in the unborn fetus, prostaglandins are free to exerttheir effects. Once parturition occurs however, and the neonatal blood becomes well oxygenated, prostaglandins are able to exert little or even no effect.

The suppression of ductal response to PGs under aerobic conditions is interesting in that this effect is opposite of that evidenced in other tissues. Coceani and Olley[50] suggest that different sites or pathways mediate the actions of prostaglandins and also that the effect is not due to intrinsic properties of ductal smooth muscle since its activity is little affected by lack of oxygen when stimulated by other chemical mediators. When the end result is smooth muscle contraction, oxygen may be a required participant in an intervening step which may not be present in an interaction producing relaxation.

Another possibility advanced by these authors[46] to explain the mechanism of ductal reactivity to prostaglandin involves observations of ductal sensitivity to prostaglandin following depolarization of the ductal smooth muscle. Following depolarization in a high potassium medium ductal tissue exhibits decreased sensitivity to prostaglandins. They suggest that oxygen may have a direct depolarizing effect on the ductal muscle to change transmembrane potential and thereby decrease responsiveness to prostaglandins.

Human studies of ductal responsiveness to prostaglandins have demonstrated a strong dilatory effect of prostaglandins of the E series.

Several authors have reported in vivo effectiveness of PGE_1 and E_2 in maintenance of ductal patency in infants with severe congenital heart disease such as pulmonic atresia or hypoplastic left ventricle [51-54] where persistant patency of the ductal shunt was necessary for adequate oxygenation. In this group of infants, who exhibited rapid decline in arterial blood gases following oxygenation which initiates ductal closure, local infusion of prostaglandins via catheter maintains adequate temporary oxygenation. A positive response is determined by a rise of arterial pO_2 greater than 10 mmHg which may occur within 10 minutes and infusion can be continued for several days.[28] This enables proper surgical preparation to take place in this high surgical risk group.

E. The Effects of Prostaglandin Synthetase Inhibitors

Elucidation of the actions and effect of prostaglandins on the ductus led to interest in the possibility of its further manipulation in preterm infants by blocking effects of prostaglandins through inhibition of their synthesis. Prostaglandins are synthesized from 20-carbon polyunsaturated fatty acids that are present in cell membranes of all mammalian tissues. The main precursor of prostaglandins is eicosatetraenoic or arachidonic acid which, in turn, are derived from the essential fatty acid, linoleic acid.[55,56] Arachidonic acid may be metabolized via two pathways, the first involving lipoxygenases, about which little is known but which seem to be less widely distributed in the tissues, and the second involving cyclo-oxygenase (prostaglandin synthetase) which converts arachidonic acid into unstable cyclic endoperoxides. These substances may be directly converted to prostaglandins or may be metabolized via alternate pathways to other potent vasoactive products, prostacyclins and thromboxanes. Prostacyclins

are powerful vascular smooth muscle relaxants[57], about six times as potent as PGE_2, [58] and are active on nearly all systemic vascular beds.[55] Thromboxanes, on the other hand, produce marked vasoconstriction [59] and also platelet aggregation [56] before they are rapidly broken down into stable compounds.

Arachiodonic acid metabolites, prostaglandins, thromboxanes and prostacyclins, therefore have a wide range of biological actions. It is important to note however, that both aspirin and indomethacin inhibit the prostaglandin synthetase enzyme which is the first step in the cascade. Inhibition results therefore, in decreased synthesis not only of prostaglandins, but also of thromboxanes and prostacyclins.

Many prostaglandin synthetase inhibitors have been identified[60] and trials with a number of substances have been attempted using prostaglandin synthetase inhibitors to prevent PGs from exerting their dilatory effects on the ductus and producing constriction of the vessel. Chloroquine was shown in one small series [61] to produce ductal closure within 24 hours after its administration to three infants who had been in CHF for up to 5 weeks. Resolution of the patent ductus arteriosus was confirmed by catheterization and the infants were all discharged without surgical ligation. Heymann and Rudolph [62] have demonstrated the ability of acetylsalicylic acid, also a prostaglandin synthetase inhibitor, to close the ductus of fetal lambs in utero. This was shown by measurement of various hemodynamic parameters across the ductus with the use of intra arterial fetal catheters and retrospectively

with anatomic dissection.

Other investigators [23,63] have produced similar intra-uterine responsiveness to aspirin and indomethacin in lower species as well.

Several case reports have been published [64,65] in which alterations in fetal vasculature were noted secondary to maternal ingestion of either salicylates or indomethacin, both of which are known to cross the placental barrier. Maternal ingestion of these substances may constrict both the ductus and the pulmonary vascular bed, which can lead to significantly increased pulmonary vascular resistance, right to left shunting at the atrial level, and even increased perinatal mortality [65,66] secondary to inhibition of prostaglandin synthetase in the developing fetus.

Coceani et al [67] has compared the effectiveness of two structurally different prostaglandin synthetase inhibitors, eicosatetraynoic acid (ETA) and indomethacin. While both were capable of contracting an isolated lamb ductus, the effect of indomethacin was greater at a given dose.

For the most part there has been relatively greater clinical and experimental application of indomethacin than of the other prostaglandin synthetase inhibitors. Indomethacin produces a potent ductal constrictor response in vitro [47,67] and in vivo [23,51,63,68,69] and, compared to salicylic acid is able to inhibit prostaglandin synthesis at one-tenth the concentration.[60] The contractile tensions generated in the ductus by indomethacin are equivalent to those produced by exposure of the tissue to oxygen. These effects have been reproduced in a wide variety of species, including man, and have been achieved with doses as little

as .005 mg/kg.[68] Increasingly wide clinical application of indomethacin is now being made in treatment of patent ductus arteriosus in premature infants, but at this point still retains the status of an experimental drug with its own risks and specific indications.

V. Epidemiology

A patent ductus is present in about .04% of the term newborn population.[20] However a number of patient sub-populations, in addition to the premature group, have been described in whom identifiable factors are present that correlate highly with failure of the ductus to close.

Structural abnormalities in the ductus may be due to viral [70-72] or to genetic [11,73] mechanisms. Patterson has bred a line of poodles in which there is greater than an 80% incidence of patent ductus arteriosus.[74] These ducti show elastic tissue replacing normal smooth muscle and are inhibited from constriction to a degree proportional to the amount of replacement.[28]

At high altitudes, patent ductus arteriosus becomes an increasingly common finding. Studies have shown that at altitudes greater than 4000 meters, that incidence of patent ductus arteriosus is 18 times greater than at sea level.[75,76] Up to 31% of patients with patent ductus arteriosus admitted to a Lima Peru hospital came from an area in which only 2% of the population lives. It is probable that this circumstance results from the decrease pO_2 of arterial blood which acts to maintain patency of the ductus.

VI. The Special Problem of PDA in the Premature Infant

One of the strongest associations with presence of a patent ductus has been in premature infants, [77-79] especially those weighing less than 1750 grams where the incidence is 15%, [20] as opposed to .04% in the overall newborn population. [20]

Failure of ductal closure in the premature may be related to persistently low oxygen tensions in the premature infant, [18] immaturity of enzyme systems blunting ductal responsiveness to normal physiological stimuli, [37] decreased responsiveness of ductal smooth muscle to oxygen,[17] or persistent elevations of prostaglandins. [69]

A. Physiological Considerations in the Premature Infant

The development of congestive heart failure in the premature infant with patent ductus arteriosus is contributed to by a number of factors that make the problem unique to this population. Physiological responsiveness may be modified by myocardial, neurogenic and hematologic variables.

In the first instance, the characteristic Frank-Starling relationship that describes the greater contractile response of the heart to increases in volume presentation has been shown to be depressed in the fetal heart when compared with the adult.[80] The reduction in tension generated by the fetal myocardium may be due to a reduction of contractile tissue per unit of muscle mass. This is a function of decreased number of sarcomeres and an increased proportion of noncontractile tissue (i.e. nuclei and mitochondria) in the fetal myofibrils.[81] Reduced myocardial compliance in the newborn may also contribute to decreased myocardial response.[82]

Another factor contributing to myocardial failure is the lack of time preceeding volume loading to enable the neonatal left ventricle to

achieve hypertrophy in response to an increased work load. Gradual increments in myocardial work requirements are usually followed by compensatory muscle hypertrophy to cope with the increased demand. The rapid reduction in pulmonary vascular resistance, plus the left to right ductal shunt, both combine to quickly present the left ventricle with very large volumes before it has even had time to achieve normal physiological hypertrophy in the post-natal period.[11] A more gradual evolution of changes would perhaps allow the ventricle to better handle the volume load.

Finally the high resting cardiac output of the newborn heart is necessary to provide the requisite high oxygen demands of the infant. This results in a limited capacity to further increase its already high response when presented with the volume loading present in a left to right ductal shunt.[83]

The possibility of immature myocardial sympathetic innervation has been suggested as a cause for reduced ventricular response,[84] since significant growth continues to occur in the final weeks of gestation and up until several weeks after birth. This could contribute to reduced ability to respond to stress. Klopfenstein and Rudolph[83] have shown however, that significant sympathetic action does influence the neonatal myocardium, but whether this is from direct sympathetic stimulation or secondary to circulating catechols is not clear.

Hematologic parameters that may influence myocardial response in the premature infant with patent ductus arteriosus are a reduction of the pressure differential between the aorta and left ventricle due to 1) a decrease in aortic diastolic pressure secondary to the runoff from

a patent ductus, and 2) elevation of left ventricular end diastolic pressure due to the increased left ventricular return. This combination of factors may decrease the amount of coronary blood flow and result in subendocardial ischemia and a decrease in ventricular function. Also, since coronary blood flow occurs mainly in diastole, the tachycardia which is frequently present may decrease the amount of time spent in diastole per unit time.

When variables relating to hemoglobin, such as the normal decrease that occurs in the neonatal period, and the high percentage of fetal hemoglobin which gives up less O_2 to the tissues, are superimposed on the above factors compromising coronary blood flow, it is apparent that oxygen supply and myocardial function may be serverely compromised in these premature infants. These variables define a unique set of circumstances that impose difficult demands on the neonatal cardiovascular system, and predispose to the development of congestive heart failure.

A clinical variable in the development of congestive heart failure may be disparities in fluid administration which may contribute to the development of signs and symptoms of a patent ductus.[85,86] Infants who received mean daily fluid volumes of 189 ml/kg/24 hrs. had a higher incidence of patent ductus arteriosus than did a control group who received only 144 ml/kg/24 hrs. In addition, diuresis after excessive fluid administration was associated with improvement in symptoms.[86] Other authors have also shown that higher volumes of fluid administered to premature infants is associated with both an increase in the LA/Ao ratio, and an increase in pulmonary venous return.[89] While there is no prospective data to suggest that greater amounts of

fluid are administered at those centers where many ducti are diagnosed,[88] these results do imply that increased intravascular volumes may contribute to maintaining ductal patency.

B. Respiratory Distress Syndrome Complicating PDA In the Premature

The incidence of patent ductus arteriosus rises even higher in those infants who, in addition to being premature also have respiratory distress syndrome (RDS),[20,89] and may be present in as many as 45%.[90]

The coexistance of patent ductus arteriosus with premature infants who have respiratory distress syndrome is notable both from the point of view of its increased prevalence in this population, and from the difficulties arising in the medical management of the combined disorder. In addition to the possible mechanisms mentioned above that may contribute to persistent patency of the ductus, respiratory complications associated with pulmonary disease superimpose additional factors in an already compromised infant.

Neal and associates [19] have viewed the infant with patent ductus arteriosus and RDS perched on a delicate balance with respect to a number of variables that may result in clinically significant symptoms. There is an age dependent variability in the ratio of pulmonary arterial musculature to lung parenchyma that is lowest in infants less than 21 weeks gestation, and increases gradually up until birth. With less vascular smooth muscle, less pulmonary vascular resistance is achieved and hence, a greater left to right shunt may be seen. With increased

left to right shunts, a higher incidence of congestive heart failure is likely, which further compromises the pulmonary status. This is especially likely to occur in neonates whose high resting cardiac output limits their ability to augment output in response to changes in volume.[83]

Respiratory distress syndrome on the other hand, may result in acidosis, hypercarbia, and hypoxia, all of which tend to increase pulmonary vascular resistance. In addition, it has been shown that distention of the main pulmonary artery, as would occur with a large left-to-right shunt, produces a reflex vasoconstriction in the pulmonary vascular bed,[91] which together with the above factors, further predisposes to development of pulmonary edema. This may be further augmented with requisite ventilatory assistance and its concomitant positive end expiratory pressure, continuous positive airway pressure and frequent atelectasis.

Johnson et al [92] have demonstrated the presence of a metabolic acidemia within one hour after onset of ductal shunting in very premature infants, which was related to a significant decrease in lower extremity perfusion secondary to the shunt. Infants in whom the shunting was not corrected developed progressive cardiovascular compromise while those in whom the shunt was corrected by ductal ligation experienced improvements in alveolar ventilation, lower limb perfusion, and lung compliance.

The ductal shunt may be right to left, balanced or left to right depending upon which of the factors that affect pulmonary vascular resistance predominate at a given time.

Lastly, the severity of respiratory distress syndrome has been shown to be positively correlated with the degree of cardiomegaly. Infants with severe RDS had significantly earlier onset of massive cardiomegaly than those with mild or moderate respiratory disease, and, as might be expected, also had higher mortality rates.[93] A decreased cardiac output in this situation further adds to the acidosis and decreased ventricular compliance and contractility already present,[94] and by elevating pulmonary venous pressure contributes to impaired respiratory function.

Other organ systems may also become secondarily involved in a situation where a large ductus drains significant amounts of systemic blood flow. A low urine output may be observed as a result of diminished renal blood flow from a poorly perfused descending aorta. Acidosis from poor pulmonary function may also contribute to renal vasoconstriction. While renal parenchymal damage has not, to this writer's knowledge, been observed as an associated complication with patent ductus arteriosus, necrotizing enterocolitis has been reported and is presumably a function of local bowel ischemia secondary to decreased blood flow from ductal runoff. The number of patients who have necrotizing enterocolitis complicated by patent ductus arteriosus range from 10 to 30%.[95]

VII. Diagnosis of Patent Ductus Arteriosus in the Premature Infant

As noted, the incidence of patent ductus arteriosus is relatively high especially in certain populations of infants and may be as much as 6 per 1000 live births.[96] While many normal and premature infants present with evidence of patent ductus arteriosus at birth or shortly thereafter this may often be a transient finding and go on to close spontaneously. The incidence of clinically significant patent ductus arteriosus that produce notable symptomatology is less than the above mentioned figure and may be diagnosed with the use of various criteria, namely the clinical setting, conventional chest x-ray and echocardiography.

A. Clinical Criteria

The development of a large patent ductus arteriosus shunt in the premature infant is associated with fairly well defined clinical signs and symptoms.[19,29,93,97,98] Since patent ductus arteriosus is the neonatal equivalent of aortic insufficiency it is not surprising that a widened pulse pressure with bounding pulses and a hyperdynamic precordium should be present. Characteristically, a harsh systolic murmur heard best along the middle to upper left sternal border is noted. The duration of the murmur is a function of the degree of left to right shunting present and does not necessarily extend into diastole if the pulmonary vascular resistance is high. The classically described continuous machinery-type murmur is not generally heard in premature infants both because the PVR may remain relatively high and because the ductus, which is still widely dilated, minimizes the amount of turbulent

flow.[99] In one series [19] it was found that of 76 patients with both respiratory distress syndrome and patent ductus arteriosus 37% or 28 had continuous murmur while 63% or 48 had systolic murmur alone. Of further significance however is the fact that congestive heart failure developed in 14 of the 28 patients with continous murmurs but in only one of the patients with systolic murmur alone. Patients with continuous murmur represented only 37% of patients with patent ductus arteriosus but 93% of those with congestive heart failure. The continuous murmur reflects the high pulmonary blood flow which largely contributes to the high output failure. Manifestations of patent ductus arteriosus in this study were cardiomegaly on chest x-ray, tachycardia greater than 160 and hepatomegaly. Other authors have included additional criteria in diagnosis of patent ductus arteriosus such as gallop rhythm, tachypnea, and rales.[20] As the degree of shunting increases and contributes to existing congestive heart failure, apneic episodes and bradycardia become more frequent.[99]

While there is variability among observers upon what to include as diagnostic criteria in determining patent ductus arteriosus, there may also be variability of signs in the same infant.[28] Rapid changes in murmurs, pulses and arterial blood gases often occur, and can complicate the clinical picture. An infant who becomes hypoxic from fatigue or from respiratory distress syndrome may in a matter of minutes increase his pulmonary vascular resistance and decrease the intensity of his murmur without changing the anatomic lesion, and can lead to interobserver inconsistencies in reporting of clinical status.

Recently it has become apparent that another group of infants are seen possessing a "silent" patent ductus arteriosus, where it can be shown that a ductal shunt exists, sometimes in the presence of marked CHF, but where the infant lacks the characteristic murmur of an open ductus.[93,100] Thibeault et al [93] demonstrated patent ductus arteriosus with single film aortography and showed that of 27 infants with large shunts at 39 hours of age, 22 (81%) did not have concomitant murmurs and 10 of these never developed a murmur at all. The concept of the silent ductus was further elaborated by Allen et al [100] who used an echocardiographic contrast method to examine 33 consecutive premature infants with a mean weight of 1370 gms. 30/33 (91%) of these patients showed positive evidence of shunting and 24/30 (80%) initially had no murmur at the time shunting was noted. Of these 24 patients, 11 (46%) remained without evidence of murmur, despite development of CHF in 3 and echocardiographic demonstration of significant ductal shunting in all of them. It is likely that the incidence of the silent patent ductus arteriosus is much greater than formerly believed, and should therefore be carefully evaluated in a premature infant with refractory respiratory distress syndrome.

B. Chest X-ray

Conventional roentgenography is an important adjunct in diagnosis of patent ductus arteriosus but may not be conclusive until some degree of CHF and cardiomegaly is present. Radiographic findings of patent ductus arteriosus usually consist of prominent pulmonary vasculature evidence of pulmonary edema ranging from haziness of the lung fields to complete white out,[98] but this would not be expected to be a different picture than would be seen in CHF of other etiologies. These findings

may become more ambiguous if intrinsic pulmonary disease is already present and are more reliable if there is patent ductus arteriosus without underlying lung involvement.[101] In some instances, radiographic findings may be the first clinical evidence of ductal shunting and may present even before the murmur is heard.[93] Some investigators have attempted to define the magnitude of the shunt in terms of a cardiothoracic ratio greater than 60% or more specifically if this ratio increases by .05 or more on sequential radiographs.[102] Others [101] have pointed out the difficulties in these radiographic criteria due to the variable cardiothoracic ratio in the newborn especially with the presence of assisted ventilation and its positive pressures.

C. Echocardiography

In contrast to the relatively more subjective diagnostic criteria available with conventional chest x-ray or the risks attendant with invasive catheterization procedures, echocardiography has been able to provide noninvasive objective assessment of the left to right shunt present with patent ductus arteriosus. Increased shunting results in greater pulmonary venous return to the left atrium (LA) and this, in turn, ultimately results in an increased LA size as it distends to accommodate the greater return. Since there are logistical difficulties in standardizing LA size for a given age group, particularly in premature infants, [103] many authors have adopted the method of comparing the LA size to that of an adjacent fixed size structure, namely the aortic root diameter (AO), which normally results in a constant ratio when the two are compared.[101,103,106] This is expressed as the LA/AO ratio and in normal controls is less than 1.1, varing between .71 and .86 in three series. [101,103.106] The variations in mean ratio observed are mainly a function of methodological differences. [103]

Infants with a large duct have significantly greater LA/Ao ratios. Silverman, [103] who cites a mean LA/Ao in normal controls of .86 showed a mean ratio of 1.28 in infants with patent ductus arteriosus (p less than .01); ratios of greater than 1.15 were also always associated with significant cardiac failure. In infants who are managed either medically or surgically the LA/Ao ratio declines to within normal limits within 24-72 hours after clinical or surgical closure of the ductus is accomplished.[97,103,105,106] Serial echocardiographic measurements are of use in monitoring therapeutic response and resolution in both medical and surgical corrections, particularly in infants with overlying pulmonary disease.[101] Diagnostic echocardiographic studies are therefore able to document increased left to right shunting at the ductal level although other situations would also produce the similar picture of increased LA/AO ration, i.e. mitral insufficiency or increased shunting at the atrial level from right atrium to left a in pulmonic stenosis or atresia. Infants serve as their own controls, and post treatment studies, if demonstrating decrease in the previously elevated ratio, indicate resolution of the defect.

Since the LA/Ao ratio is an indication of volume overload it should be noted that heart failure from other causes besides patent ductus arteriosus may result in a similar picture, although in prematures patent ductus arteriosus is probably the most common source.[103] It was noted in one series [101] that the left ventricular end diastolic dimension was more frequently abnormal than the left atrial dimension at the time of first measurement, which is probably a function both of

the increased volume and the compensated high output failure state. Hirschklau et al [104] isolated a group of 7 out of 31 consecutive patients with patent ductus arteriosus in whom all clinical and radiographic criteria, except for abnormal LA/Ao ratio (mean ratio =.68), suggested presence of a large left-to-right patent ductus arteriosus shunt. The 7 infants did not differ from the other 26 in whom there was an increased LA/Ao ratio. Even though the ratio was normal to begin with, in 5/6 infants in whom it was measured after pharmacological or surgical closure, the ratio decreased. The left ventricular end diastolic diameter was however elevated when symptoms were at their height, [104,105] and this too decreased after shunting was interrupted. The authors propose that this group of infants may represent an altered LA configuration in which the enlargement occurs exclusively in a cephalocaudal axis rather than an anteroposterior one. The altered atrial configuration may also be due to sternal retractions which causes flattening of the left atrium. [107] The LA/AO ratio may therefore miss some infants with a PDA shunt if its value is used as the absolute diagnostic criterion. In those infants with clinical signs of shunting nevertheless, ventricular size on echo may help to corroborate the clinical impression.

Allen et al [100] has reported a new echocardiographic technique utilizing injection of nonviscous contrast material (saline, D5W, or the patient's own blood) through an umbilical catheter with its tip located above the diaphragm. In the presence of a patent ductus arteriosus the transverse aortic arch as well as the right pulmonary artery were opacified while in the absence of patent ductus arteriosus only the transverse aortic arch showed the contrast. The study is both safe and sensitive and is very effective especially in demonstrating the silent

patent ductus arteriosus. Risks of performing this new technique are probably those of the presence of a high umbilical catheter itself.[108]

VIII. Treatment of the Patent Ductus Arteriosus

A. Medical and Surgical Management

Since the patent ductus will often close spontaneously[20] medical management may bide enough time for this to occur.[19] Usually this involves treatment of CHF with digitalis and diuretics (furosemide; Aldactone may be added to avoid electrolyte imbalance),[4,20,89,109,110] fluid restriction,[4,29,109] and blood transfusions for hematologic maintenance (hematocrit>35) if necessary.[20,31]

Coexistance of patent ductus arteriosus with respiratory distress symptoms adds the seriously complicating variable of adequate gas exchange and these infants must be maintained with ventilatory assistance. Provision of adequate paO_2 within the range of 50-70 mmHg should be achieved, but often steadily increasing FIO_2 is required to keep paO_2 constant.[20] $PaCO_2$ is also difficult to control and dangerously high levels may presage respiratory and cardiac decompensation.[20,111] It is generally agreed that respirator dependence for prolonged periods of time is harmful and that inability to wean from the respiratory is a surgical indication for patent ductus arteriosus ligation.[112]

Pulmonary sequela are quite high in infants with the combined disorder requiring ventilatory assistance, and one review of the literature encompassing 13 separate reports, notes that of the infants who died after surgical repair of patent ductus arteriosus, 2/3 succumbed as a result of pulmonary complications, with bronchopulmonary dysplasia being the most common.[112] Others have emphasized the importance of early resolution of patent ductus arteriosus, in an effort to avoid irreparable pulmonary damage.[20,89] However, it is not unequivocal as to whether or

not early interruption of the patent ductus arteriosus will definitively decrease the incidence of pulmonary disease.[112]

Optimal management will generally include close observation until signs and symptoms of CHF or respiratory distress occur. The conditions are managed with pharmacological and respiratory therapy, but the criteria for defining the moment of decisive surgical intervention is still open to some debated.[19,79,93,112,113] However, the general guidlines of worsening respiratory distress symptoms with hypercarbia, onset of CHF, and deteriorating clinical status manifest by such prominent signs as frequent bradycardia and apnea, may be adhered to.

Difference in myocardial structure and function are found between premature and term infants and effect the efficacy with which successful pharmacological treatment may be achieved. The premature myocardium has greater amounts of water and connective tissue, and less muscle fiber regularity and sympathetic innervation than that of the term infant.[80] With given fluid overload there is less compliance and hence higher left ventricular end diastolic pressures which produces earlier symptomatic CHF. It has also been shown in newborn sheep[83] that there is a decreased ability to handle a volume load in the neonate when compared to an older animal. This is probably a function of the newborn's high cardiac output as an attempt to provide a necessarily high oxygen requirement for the transition from fetal to extrauterine life. The high basal cardiac output in the newborn prevents it from significantly increasing its left ventricular output in response to a fluid challenge as might be seen in left to right ductal shunting.

As a result of these parameters, proportionately greater symptomatic relief may be achieved with diuretics than with digitalis glycosides. [28] Berman [28] has shown that a difference in response to digitalis exists between fetal sheep and ewes and that the difference in drug sensitivity is an age related function. There may also be an age dependent variability in prematures of varying gestational ages. This inconsistent sensitivity is superimposed upon a wide range of capacities dependent upon competent renal functioning for metabolizing and excreting the drug, which can potentially result in toxic effects in as many as 30% of infants treated with digitalis.

B. Indomethacin

Surgery as a treatment modality clearly carries tremendous risks for this population who are poorly equipped to handle the stress and potential infection thoracotomy entails. While mortality alone in some series may be as high as 50% [114] other authors have reported very successful results. [89] This appears to be somewhat dependent upon the center at which the procedure is performed. Long term morbidity may also be quite high[111] and is a serious consideration.

The ability of indomethacin to close the patent ductus has been discussed and provides a means of medically treating a serious problem in a manner that is hopefully safe and effective. In a report by Friedman, Heymann and Rudolph [4] of 50 premature infants treated with indomethacin for patent ductus arteriosus, there was failure to close the ductus in only one. Neal[25] has reported significantly less successful results achieving permanent ductal closure in only 2 of 11 patients but his population was somewhat older when first treated and was also given repeat doses at intervals of 2 days to 2 weeks instead of within 24 hours as proposed by Friedman et al.

Since indomethacin is not without toxicity it is important to identify various risk factors to determine those patients for whom indomethacin would not be appropriate therapy. The risk factors primarily involve 1) bleeding tendency, 2) renal compromise and 3) hyperbilirubineamia. It has been implicated as a cause of a sudden death syndrome in 4 children but only after prolonged and high dose therapy.[115]

Indomethacin has been specifically noted to inhibit platelet aggregation. These effects may be increased in the neonate since indomethacin metabolism is prolonged and its half life extended possibly secondary to immature hepatic and/or renal excretory systems.[116] While clotting studies (PT,PTT) have usually been used to monitor hematologic toxicity, [97] the lack of a role of prostaglandins in these functions [116] may indicate that bleeding time or platelet aggregation are more accurate reflections of potential hematologic disturbances. In addition, since indomethacin is bound tightly to serum albumin, [117] elevated levels of bilirubin which is also bound to serum albumin, may result in relatively greater concentrations of free indomethacin in the serum. This in turn would conceivably allow indomethacin to exert a greater anti-platelet effect and result in bleeding. No complications from elevated bilirubin levels have been reported as a result of treatment with indomethacin, and levels of indirect bilirubin greater than 10 mg% were, at first, considered contraindications to therapy.[118] A recent study has indicated that indomethacin may be a weaker displacer of bilirubin from albumin than originally thought which implies less hazard in producing iatrogenic hyperbilirubinemia.[119]

PGE is synthesized within the renal medulla and plays an important role in defending renal function against excessive activity of the salt and water conserving system and the adrenergic nervous-renin-angiotensin-antidiuretic-hormone-system. It also acts as a local hormone to dilate renal blood vessels and therefore effects intrarenal distribution of blood flow [120] especially under hypoxic conditions. [121] Indomethacin has been noted to induce transient renal failure in infants receiving it [25,97,122] and this has been manifested by increased BUN and creatinine and transient oliguria. In no instance however have the effects persisted and infants up to 13 months after therapy have been noted to have normal renal function. [4,123] The effect of indomethacin on renal function appears to be dose related. [109,124] Infants who received a single dose of either .1 or .3 mg/kg indomethacin had no signs of renal insufficiency while infants who received 3 doses of .3 mg/kg all had transiently elevated creatinine and decreased urine output. Groups of lambs receiving both high and low dose indomethacin had significantly decreased blood flow at 4 hours but only high dose animals had decreased renal blood flow at 12 and 24 hours. While GFR was unchanged in both groups, urine flow was decreased in the high dose group and this latter parameter is utilized in the clinical situation to indicate that the drug has been adequately absorbed.

Therefore, if the parameters of bilirubin metabolism, coagulation and renal function are found to be within normal limits the infants may be a candidate for nonsurgical indomethacin induced closure of the patent ductus. It is recommended [4] that .2 mg/kg of indomethacin be administered orally by nasogastric tube, with careful monitoring of all cardio-pulmonary clinical and laboratory variables mentioned, esepcially bleeding,

hyperbilirubinemia and derangements in renal function. If rapid changes in oxygen requirements concomitantly occur due to better perfusion, precautions against retinal arterial vasoconstriction must be considered. As many as 60% of infants may respond with ductal closure after only one dose but if closure has failed or has been inadequate, a repeat dose of indomethacin may be given between 12 and 24 hours after the first dose and then repeated once again if necessary for a total of 3 doses (.6 mg/kg total). The second and third doses are cumulative [29] due to the longer half life of indomethacin in the neonate.[116] A total dose greater than .6 mg/kg does not increase the success rate [88] and infants who fail to close their ductus after this dose has been reached are candidates for surgical ligation.

At this point it is pertinent to note that a large scale twelve center co-operative study has recently begun to assess the efficacy and role of indomethacin in the treatment of the patent ductus arteriosus in premature infants. This study is designed to assess the impact both of indomethacin and of conventional modes of treatment for the patent ductus arteriosus, and controls for the many clinical variables that have previously been discussed which may affect such interpretation, by strict double blind randomization of the patient population. The results of this study will begin to be reported in 1982.

MATERIALS AND METHODS

Twenty-eight premature babies admitted to the Newborn Special Care Unit at Yale-New Haven Hospital who were diagnosed as having a symptomatic patent ductus arteriosus, and who were treated with indomethacin in an attempt to correct their lesion are reported.

Data concerning their hospital course, treatment and response to therapy was gathered retrospectively from the medical records, and includes information on all babies administered this treatment during the sixteen month period from July 1977 through October 1978.

Infants were cared for in closed Air-Shields intensive care isolettes. Standard fluid therapy for infants in the Newborn Unit consisted of 60, 80, and 100 cc/kg/day on days 1, 2, and 3 of life respectively, and was increased to 120 cc/kg/day, or as tolerated, from day four on. Signs of congestive heart failure or of a patent ductus arteriosus resulted in restriction of fluid to 80-100 cc/kg/day. Anemia was treated with transfusions of packed red blood cells in 5-15 cc increments to maintain the hematocrit greater than 30%, and electrolytes were given as need in I.V. solutions to maintain appropriate values.

Respiratory distress syndrome was present in the majority of infants in this study and was diagnosed on the basis of prematurity, lack of other causes to account for respiratory difficulty, clinical evidence of retractions and grunting, persistently elevated FIO_2 requirements in order to maintain adequate PaO_2, and chest roentgenograms with characteristic diffuse granular infiltrates and air bronchograms.

Ventilatory requirements were met with a Bournes Pressure Twin Cycle Respirator (Model BP200) and endotracheal intubation to provide airway access and positive end expriatory pressure (PEEP), or with nasal prongs and continuous positive airway pressure. PEEP was given at pressures between three and seven cm. H_2O, and intermittent manditory ventilation rates and FIO_2 being adjusted as needed to maintain adequate PaO_2. Frequent arterial and/or capillary blood gas determinations were made to monitor progress and response.

Infants were first suspected of having a patent ductus arteriosus when a characteristic continuous or systolic murmur was heard, usually within the first few days of life, at the left upper sternal border. At the time the murmur was heard, associated signs of aortic run-off across a PDA were noted. These signs included bounding pulses, hyperactive precordium, hepatomegaly, tachycardia (>160), and spillover of the murmur into diastole. Radiographic signs of shunting included pulmonary vascular engorgement, and cardiomegaly. On the basis of these findings a presumptive diagnosis of PDA was made, and in all instances, one or more echocardiograms were obtained to assess the degree of left-to-right shunt present by calculating the LA/Ao ratio.

Echocardiographic studies were performed using a commercially available Picker ultrasonoscope. In order to standardize echocardiograhic measurements, leading edge criteria for determination of intervals was employed. This method takes into account the finite thickness of the lines produced by echo recordings, and uses as points of measurement that edge of a given line that lies most anterior on the echo strip.

With the transducer placed in the third or fourth intercostal space at the left sternal border, the left ventricular chamber is first identified. A sweep is then made from the left ventricle to the left ventricular outflow tract, encompassing within it the mitral as well as the aortic echoes. Using the mitral valve as a reference point, the adjacent aortic-root and left atrial dimensions are identified. The left atrial diameter is calculated in end-diastole, its largest value, which is determined by comparing the echocardiogram with the QRS complex of a simultaneously obtained EKG.

The absolute criteria for an LA/Ao ratio large enough to be evidence of a significant left-to-right ductal shunt necessitating indomethacin therapy was taken to be 1.3, but this value was not rigidly adhered to if the clinical situation implied serious cardiac compromise, or if serial echocardiograms showed a sequential change of .3 between measurements. In some infants with evidence of significant shunting medical therapy consisting of lasix and/or digitalis was instituted. In others, indomethacin was given without first attempting medical management.

Before giving indomethacin, consent was obtained from the parents of each infant as authorized by the Human Investigation Committee. Laboratory studies were also routinely obtained prior to indomethacin for each infant and included hemoglobin, hematocrit, platelet count, white cell count, bilirubin, blood urea nitrogen, creatinine, prothrombin time, and partial thromboplastin time. Evidence of gastrointestinal bleeding, coagulation defect, thrombocytopenia, elevated BUN/Cr (<30/1.8), or bilirubin greater than 10 mg%, were considered contraindications to indomethacin.

Indomethacin was administered via nasograstric tube or as a rectal suppository in all infants in a dose of .3 mg/kg and was repeated up to three times at intervals of eight hours in all but one infant in whom six doses were given over a 48 hour span. Response to the drug was assessed by frequent physical exam and change in cardiac murmur, and with follow-up echocardiograms looking for change in the LA/Ao ratio. In some infants in whom complete regression of the murmur did not occur, spontaneous disappearance was sometimes noted a period of time after the drug was given. Those infants in whom no change in status was noted, or in whom reopening of the ductus occurred within initial regression of the murmur were candidates for retreatment with indomethacin with the same dosages, routes of administration, and intervals. Follow-up laboratory data included BUN and/or creatinine, hemoglobin, hematocrit, platelet count, and electrolytes. In some infants, intractible congestive heart failure, worsening pulmonary status, and persistance of the murmur constituted treatment failure, and necessitated surgical ligation of the ductus.

RESULTS

During the sixteen month period from July 1977 through October 1978, a total of 1,461 babies were admitted to the Newborn Special Care Unit at Yale-New Haven Hospital. Of these, 264 (18.1%) weighed less than 1,750 grams. Twenty-nine (11%) of the infants weighing less than 1,750 grams developed a symptomatic patent ductus arteriosus during their hospitalization, and 28 of these patients were treated with indomethacin.

All of the babies in this study were premature, and had gestational ages ranging from 26-33 weeks (X=29.8 weeks), with 17/28 (61%) of the infants having a gestational age of 30 weeks or less. Weights ranged from 860-1,790 grams (X=1293 grams), with 48% weighing less than 1,250 grams. There were an equal number of males and females (14) in the group. This data as well as presence or absence of RDS and other diagnoses made concurrently during their hospitalization are shown in Table I. A ventricular septal defect was also present in two patients, and RDS was noted in 24/28 infants (86%).

All infants in this study required some form of respiratory support during their hospitalization. The maximum respiratory requirements needed by the patient group, as well as the maximum FIO_2 required within each group, and the duration they received the most invasive respiratory support are included in Table II. Also noted are the pulmonary complications detected radiographically and clinically within each group. As would be expected, infants who required endotracheal intubation for ventilatory support with PEEP had the greatest incidence of pulmonary complications.

TABLE I. Characteristics of 28 Premature Infants with PDA

Case #	Sex	Gestational age (weeks)	Apgars 1'/5'	Birth Weight	RDS	Other*
1	F	33	7/8	1590	+	
2	M	32	5/7	1140	+	IVH, apnea, pulse drops
3	M	29	7/8	1390	+	apnea, hyperbilirubinemia NEC
4	F	32	3/7	1721	–	birth asphyxia, apnea
5	F	32	2/7	1400	+	ABO incompatibility, IVH
6	F	30½	?	1380	+	apnea, hyperbilirubinemia
7	M	31	8/8	1740	+	PVH, hyperbilirubinemia
8	F	29	5/3	1075	+	–
9	F	32	5/?	1330	+	hyperbilirubinemia
10	M	26	6/8	860	+	apnea, NEC
11	F	29	6/6	992	+	apnea
12	M	28	1/2	1580	–	birth asphyxia
13	F	28	6/8	1300	+	apnea, BPD
14	F	30	0/4	1729	+	apnea
15	F	33	6/6	1790	–	tracheoesophageal fistula hyperbilirubinemia
16	M	31	7/9	1300	+	hydrocephalus
17	M	28	6/6	1000	+	PVH, NEC, hyperbilirubinemia
18	F	29	0/?	1080	–	PVH, birth asphyxia, apnea, hyperbilirubinemia
19	F	28	6/7	1030	+	apnea
20	F	31	6/9	1160	+	BPD, pneumonia, corpulmonale
21	F	29½	2/4	1250	+	anemia, ?NEC
22	M	30	6/8	1500	+	–
23	M	28	1/5	950	+	triplets, inguinal hernia
24	M	28	1/5	1490	+	triplets, anemia hyperbilirubinemia
25	M	28	5/?	960	+	subarachnoid and IVH VSD
26	M	28	6/?	1040	+	BPD
27	M	29½	3/5	1120	+	birth asphyxia, anemia, apnea, hyperbilirubinemia
28	M	31	7/8	1300	+	anemia, apnea, VSD, hyperbilirubinemia

PVH- paraventricular hemorrhage

*IVH - intraventricular hemorrhage, NEC-necrotizing enterocolitis
BPD-bronchopulmonary dysplasia, VSD - ventricular septal defect

TABLE II

Maximum Respiratory Support Required by 28 Infants with PDA

	No. of patients	%	Max. FIO_2	Duration	Complications		
O_2 only	5	18	50	0-3 days	apnea pneumonia pneumothorax	3 1 1	(50%) (17%) (17%)
CPAP	2	7	52	1-3 days	apnea	2	(100%)
Mechanical Ventilation	21	75	100	2-49 days (X=16.2)	apnea pneumonia penumothorax interstitial bronchopulmonary dysplasia (BPD)	6 3 9 5 6	(29%) (14%) (43%) (24%) (29%)

Overall, there were only 2 deaths out of the 28 infants studied (7%). Both infants were born at a gestational age of 29 weeks, and had severe RDS requiring vigorous respirator support. One infant (case 3) had had episodes of apnea and bradycardia prior to indomethain. Necrotizing enterocolitis had been questioned but not definitively diagnosed, and antibiotics were being given for presumed sepsis. One dose of indomethacin was given on the day prior to death with a decrease in the intensity of the murmur from Grade 4/6 to 2/6. One hour before a second dose of indomethacin was given on the following day, the infant became bradycardic but responded well to bagging. Thirty minutes later he seemed clinically stable, and received a second dose of indomethacin, .3 mg/kg per rectum and thirty minutes following that, became bradycardic and was unresuscitatable.

The other death (case 9) had been unresponsive to medical management, to three courses of indomethacin, had persistent respiratory distress syndrome and subsequent BPD secondary to prolonged respirator dependence, and ultimately underwent ductal ligation. Subsequent to surgery it was impossible to wean the child from the respirator, and persistently falling PaO_2 despite maximum ventilation with 100% O_2 led to the demise.

The clinical and radiographic evidence of left-to-right shunting that was ascertained for each infant is summarized in Table III, along with the number of patients in whom each item was observed and the percent of total exhibiting the finding. Since initial suspiciion of a patent ductus was raised with the presence of a new murmur, it is not surprising that 100% of the patients in this study exhibited a systolic murmur. However, the classical continous machinery-type murmur was present in only 68% of patients.

TABLE III

Clinical Signs of Patent Ductus Arteriosus

	No. of patients	%
Physical Exam		
Bounding Pulses	23	82
Hyperactive Precordium	21	75
Hepatomegaly	14	50
Tachycardia	22	79
Systolic Murmur	28	100
Murmur extending into Diastole	19	68
Radiographic		
Increased Pulmonary Vasculature	17	61
Cardiomegaly	16	57

Congestive heart failure manifested radiographically by cardiomegaly, pulmonary vascular redistribution, and/or pulmonary edema was present in 19 patients. Of these 19, 13 (68%) also had a continuous murmur. Six patients with a continuous murmur did not have radiographic signs of congestive heart failure.

Medical therapy was implemented in 16 of the infants in this study. Of these 16, 13 (81%) had radiographic evidence of congestive heart failure, while three did not. All 16 failed medical management and went on to receive indomethacin.

A murmur suggestive of a patent ductus arteriosus was heard between 1 and 11 days with a mean age at onset of 4 days. Congestive heart failure was present in 19 patients (68%) with a mean age at onset of 9 days. Indomethacin was given between 0 and 27 days after the murmur was first noted with a mean span between onset of the murmur and administration of the drug of 5.7 days. In all but two instances, initial administration of indomethacin was associated with at least temporary improvement in the murmur. In case 1, no change was noted in the murmur after indomethacin was given, but the murmur spontaneously disappeared on the eighth day following the drug. In case 7, lack of response to indomethacin as evidenced by a persistent murmur, elevated LA/Ao ratio, and continued radiographic picture of congestive heart failure necessitated surgical ligation of the patent ductus arteriosus.

There were 12 cases where a low grade, persistent murmur remained after indomethacin was given. One of these patients died, two were felt to have a small ventricular septal defect accounting for the murmur, and in five the murmurs spontaneously disappeared at 6, 8, 20, 22 and 63 days of age respectively. The remaining 4 infants retained a mild Grade 1/6 flow murmur that was present at discharge.

Twelve cases were observed where a recurrence of the murmur was noted after an initial response to indomethacin. The time of recurrence ranged from 1-14 days after indomethacin was given, and occurred in 5/6 infants who eventually required surgical ligation of their ductus. Thus, 42% of patients in whom a recurrent murmur was noted went on to require surgery for their patent ductus. This data is shown for all 28 patients in Table IV.

The six patients who required surgical intervention are shown separately in Table V, and represent 21% of the total group who received indomethacin. The surgical group were born with gestational ages from 28-32 weeks with a mean of 29.3 weeks as opposed to a mean gestational age of 29.2 weeks for the 22 babies who did not need surgery. Birth weights for the treatment failure group ranged from 950-1,740 grams (X=1258) which was less than the mean birthweight of 1,302 for the other patients. The mean age at which treatment failures were noted to have a murmur and were given indomethacin was day 5.0 and day 11.8 respectively, which was greater than those of the other babies, 3.6 and 8.9 respectively. All five indomethacin failures required mechanical ventilation and needed it for a mean duration of 23.8 days as compared with the mean of 11.8 days required by all other babies who needed ventilation. None of these

TABLE IV- Clinical responses to Indomethacin

				Response to Indo				
Case No.	Age murmur first heard (days)	Age onset CHF	Age Indo given (#doses)	#days before murmur absent	Change in murmur (grade)	Age murmur recurred (days following Indo)	Age retreated (# doses)	Final Outcome*
1	4	12	14(6)	8	-	-	-	m. spontaneously disappeared
2	3	-	5(3)	2	-	10(5)	-	2/6 m. (mild branch pulmonic stenosis
3	1	-	6(2)	-	4/6→2/6	-	-	died age 7 days (cardi arrest
4	3	4	6(3)	1	-	-	-	-
5	2	16	7(2)	1	-	9(2)	19(3)	persistent 1/6 flow m.
6	4	-	16(2)	1	-	18(2)	-	persistent 1/6 flow m.
7	5	3	7(3)	-	4/6→4/6	-	-	PDA ligation
8	4	4	4(1)	1	-	8(4)	8(3)	PDA ligation
9	6	14	8(3)	-	3/6→2/6	-	16(3)	PDA ligation, died from RDS
10	6	14	16(1)	-	4/6→2/6	-	-	m. spontaneously disappeared
11	5	22	7(1)	1	-	12(5)	-	2/6 VSD m.
12	7	-	24(2)	1	-	-	-	-
13	2	-	6(2)	1	-	-	-	-
14	3	-	7(2)	1	-	-	-	-
15	8	-	10(2)	1	-	-	-	-
16	4	5	7(3)	6	4/6→1/6	-	-	-
17	1	3	9(2)	1	-	10(1)	-	m. spontaneously disappeared

TABLE IV (continued)

				Response to Indo				
Case No.	Age murmur first heard (days)	Age onset CHF	Age Indo give (#doses)	# days before murmur absent	Change in murmur (grade)	Age murmur recurred (days fol-lowing Indo)	Age retreated (# doses)	Final Outcome*
18	4	4	6(3)	12	3/6→1/6	-	-	m. spontaneously disappeared
19	4	-	13(1)	1	-	18(5)	-	m. spontaneously disappeared
20	2	-	7(2)	1	-	-	-	-
21	6	2	7(3)	1	-	-	-	-
22	5	6	7(3)	-	4/6→1/6	-	-	m. spontaneously disappeared
23	2	26	29(3)	-	4/6→1/6	32(3)	26(3)	PDA ligation
24	2	20	4(3)	-	2/6→1/6	18(14)	23(3)	PDA ligation
25	11	13	19(3)	4	3/6→1/6	25(6)	26(3)	PDA ligation
26	1	3	7(2)	1	-	8(1)	-	persistent 1/6 flow m.
27	2	3	4(1)	1	-	15(11)	-	m. spontaneously disappeared
28	2	4	4(1)	1	-	-	-	1/6 VSD murmur

*Unless otherwise noted, patients were subsequently discharged home.

TABLE V. <u>Patients who Failed Indomethacin Therapy and Required Surgery</u>

Case No.	Gestational Age	Birthweight	Age murmur first heard	Age Indomethacin first given	No days on respirator
7	31	1,740	5	7	7
8	29	1,075	4	4	43
9	32	1,330	6	8	49
23	28	950	2	29	4
24	28	1,490	2	4	7
25	28	960	11	19	33
X=	29.3	1,258	5.0	11.8	23.8
Mean values for 22 patients who responded to Indomethacin					
	29.2	1,302	3.6	8.9	11.8*

*Includes only 15 other patients who required mechanical ventilation.

differences between indomethacin responders and non-responders approaches statistical significance at the 5% level when calculated by the Mann-Whitney U Test.

The response to indomethacin seems to be improved the earlier it is given in the baby's course (Table VI). In patients in whom it was given within the first 10 days of life, an 85% response rate was observed. This is to be contrasted with the response rate of 50% in patients given indomethacin between 10 and 20 days of age. Only two babies first received indomethacin when they were greater than 20 days old, and one of these responded to the drug.

Response to indomethacin as demonstrated by the LA/Ao ratio is shown in Table VII and Figure 1. It can be seen that a decrease in this ratio accompanied indomethacin administration in 21/22 (96%) cases for whom there were both pre- and post-indomethacin LA/Ao ratios documented. Overall the mean LA/Ao ratio before receiving indomethacin was 1.54, with the mean ratio after treatment being 1.17. The pre- and post-indomethacin measurements therefore approximate values one would expect to see in situations of significant left-to-right shunting, and in normal patients respectively.

Laboratory data that were available for the infants in this study showed no alteration in hemoglobin, hematocrit or platelet count attributable to indomethacin. Six patients were noted to have had transient oliguria following their indomethacin treatment, but in none of these did the oliguria persist longer than 14 hours. Urinalyses performed before and after the indomethacin dosage showed no gross abnormalities. BUN

TABLE VI

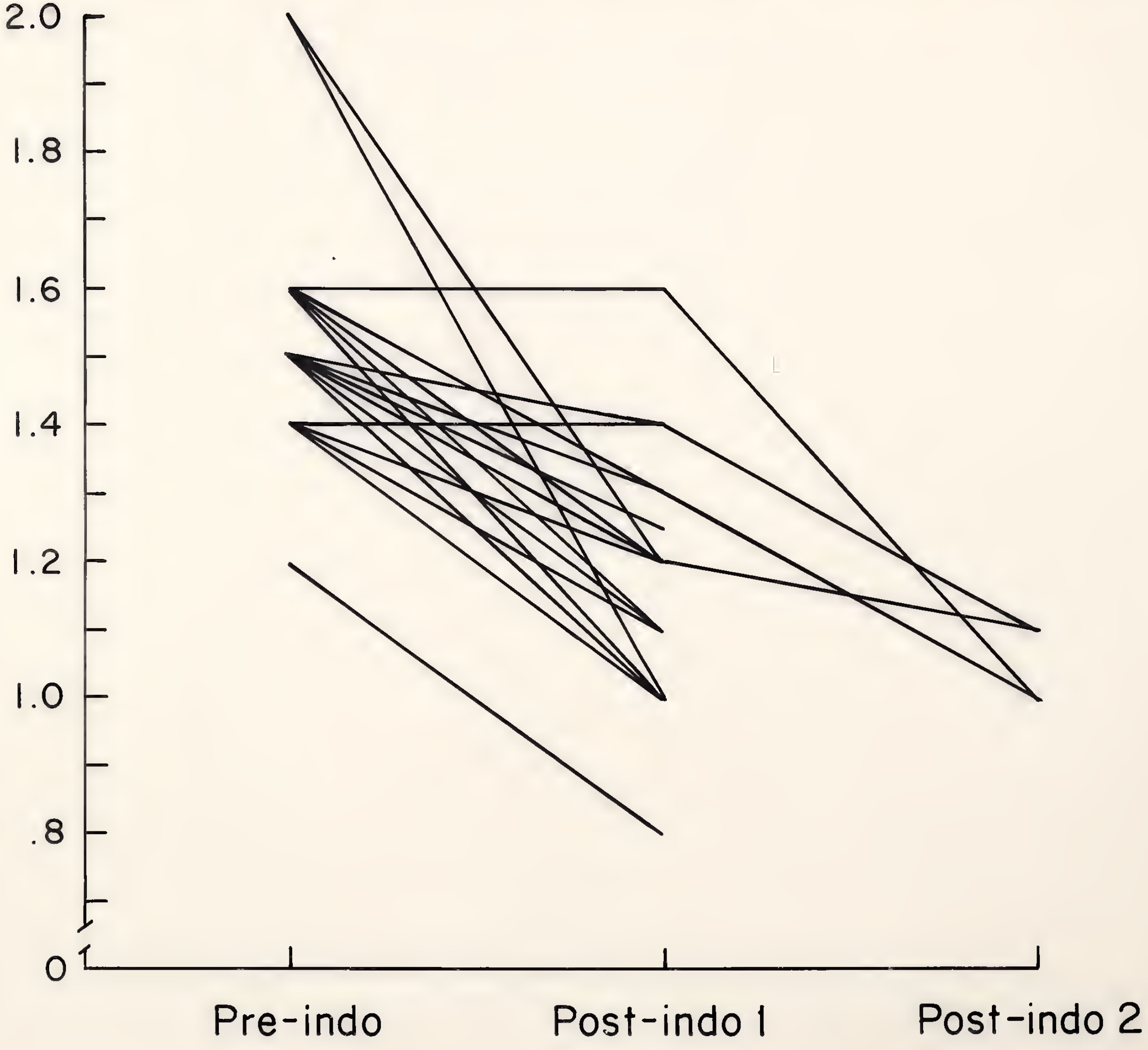
Response to Indomethacin as a Function of Age

Age Indomethacin Given	Number	Number Responding	%
0-10 days	20	17	85
10-20 days	6	3	50
20-30 days	2	1	50

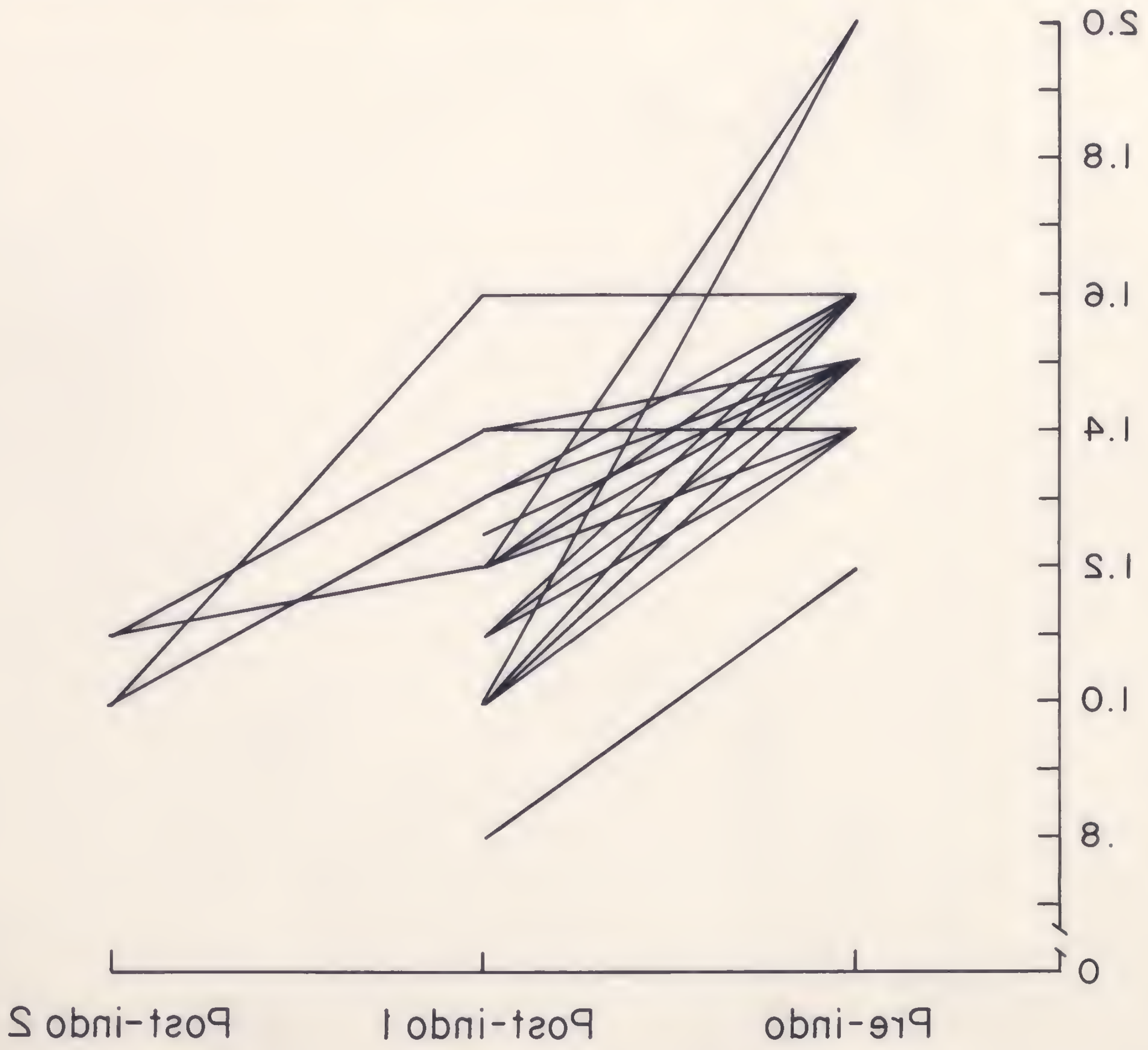
TABLE VII. Mean LA/Ao Ratios: Before and After Indomethacin

Case No.	Pre-Indo	Post-Indo No. 1	Post-Indo No. 2
1	1.6	1	
2	1.5	1.1	
3	1.7		
4	1.6	1.1	
5	1.4	1.4	1.1
6	1.5		
7	2.0	1	
8	1.6	1.6	1.0
9	1.5	1.3	1.0
10	1.2		
11	1.5	1.4	
12	1.5	1.2	
13	1.4	1.1	
14	1.4	1.1	
15	1.5	1.25	
16	1.6	1.2	
17	1.5	1.0	
18	1.5	1.3	
19	1.4	1.2	
20	1.2	.8	
21	1.6	1.0	
22	2.0	1.2	
23	1.4	1.3	
24	1.6	1.3	1.1
25	1.5		
26	2.0	1.0	
27	1.4	1.0	
28	1.6	1.3	
X	1.54	1.17	1.05

LA/Ao RATIOS FOR 22 PREMATURE INFANTS
BEFORE AND AFTER RECIEVING INDOMETHACIN



LA/Ao RATIOS FOR 22 PREMATURE INFANTS
BEFORE AND AFTER RECIEVING INDOMETHACIN



and creatinine measurements taken after indomethacin was given to those patients with transient oliguria were comparable to those values obtained before indomethacin treatment, and are shown in these six patients in Table VIII.

No evidence of abnormal bleeding occurred in the 28 patients who received indomethacin, although one patient did have guaiac positive stools following his indomethacin dosage, but it was not clear whether this was secondary to the indomethacin itself or instead was due to NEC. There was, however, spontaneous resolution of the problem and no further evidence of bleeding was noted in that patient.

TABLE VIII.

BUN/Creatinine Measurements Before and After Indomethacin in Six Infants with Transient Oliguria

Case Number	Pre-Indomethacin	Post-Indomethacin
2	24/.9	26/-
11	11/1.2	11/1.1
17	17/1.0	11/1.4
24	13/.5	15/.8
25	8/-	11/1.2
28	22/1.3	23/1.2

DISCUSSION

The concept of pharmacological manipulation of the ductus arteriosus was the result of a search for the mediators of ductal function. Early experiments by Sharpe and Larsson [49] and Starling and Elliott [47] demonstrated the contribution of prostaglandins in maintaining ductal patency. Studies were subsequently performed showing the ability of prostaglandin synthetase inhibitors to constrict the ductus, with both salicylic acid [23] and indomethacin [23,63] effective, the latter having been shown to be a much more potent inhibitor of prostaglandin synthesis. [60] Animal studies clearly demonstrated the ability of prostaglandin synthetase inhibitors to exert their effects in vivo. [62,68] The experience with ductal manipulation in human patients allowed for knowledge of prostaglandin metabolism and physiology to be used in the clinical setting. This was first attempted with PGE infusions to maintain ductal patency in infants with cyanotic heart disease[53,54] and ductal dependent pulmonary blood flow. Subsequent studies successfully achieved inhibition of prostaglandin synthetase to induce closure of the patent ductus arteriosus in premature infants where this had failed to occur shortly after birth.[97,109]

The present study has examined the results achieved at Yale-New Haven Hospital with 28 premature infants with a symptomatic patent ductus arteriosus who were treated with oral indomethacin to attempt pharmacologic closure of the shunt.

As a group, these patients possess similar characteristics to those reported for patients in other studies, [19,20,88,98] with a high

incidence of pulmonary disease and secondary medical complications that would be expected in respirator-dependent prematures.

Treatment with indomethacin resulted in a significant reduction in the symptoms of volume overload and congestive heart failure in the majority (70%) of the patients studied. This correlates well with the results observed in reviewing six other series[25,28,125-128] where a total of 114 premature infants were treated with indomethacin to close a patent ductus. Overall 86 (75%) infants were successfully treated in this manner, with a range in the individual series from 18% to 88% successful response to indomethacin.

The improvement in physiological status in this series was manifested by a decrease in cardiac activity, a decline in intensity or elimination of the murmur, and a decreased need for ventilator support. Radiologically these changes were observed as a decrease in heart size with a lessening of pulmonary vasculature congestion. On echocardiography it was shown to be a decrease in the LA/Ao ratio. In most instances significant improvement was noted within one day after administration of the drug. While some patients had minor or transient recurrence of the ductal murmur, this seemed to have no adverse impact on the clinical course.

Cases in which the murmur persisted frequently resulted in spontaneous disappearance of the murmur during the hospital course. Even in those instances where a slight murmur continued to persist, the stability of these patients as assessed by their clinical, radiological, and echocardiographic evidence makes it likely that any physiological insult as a result of this was negligible. Heymann [28]

has commented on this phenomenon and has noted that its importance relates to the fact that the end point in treatment is not necessarily complete initial closure but achievement of sufficient clinical stability to allow successful conventional management.

The role of echocardiography over the last decade has come to assume primary importance in the diagnosis of a clinically significant patent ductus arteriosus. Serial LA/Ao measurements obtained before and after treatment with indomethacin clearly substantiated the effect of indomethacin in reducing the ductal shunt. Decreased flow to the left atrium due to ductal constriction uniformly decreased the observed ratio, and correlated well with clinical improvement. Lack of a definite protocol, however, regarding the times pre-and post-indomethacin that echocardiographic assessment of the ductal shunt was to have been obtained may have contributed, in part, to the somewhat higher post-indomethacin LA/Ao ratio obtained when compared with standards previously reported.[101,103,104,109]

While the majority of patients in this study had a clinically favorable response to indomethacin, it was necessary to ligate the ductus in six, five of whom subsequently survived. These patients had severe cardiovascular and pulmonary compromise, and had shown no response to indomethacin despite several administrations of the drug. The patients in this study who responded poorly to indomethacin all required respirator support, tended to be treated at an older age, and had ducti that seemed to initially respond to indomethacin but later

reopened. In general, the decision to treat the lesion surgically was made after medical management failed to reverse persistently declining clinical status manifested by increasing CHF, FIO_2 and P_aCO_2. Increasing P_aCO_2 has been viewed as the most important parameter in deciding whether or not to operatively intervene in this, as well as other studies,[112,114] and usually occurs late in the disease course. Since this parameter may reflect severe underlying pulmonary disease, complications attributable to surgery alone are difficult to assess and have yet to be analyzed in a well controlled prospective manner in a direct comparison with medical treatment.

Although not statistically significant, it is interesting to note the tendency for infants older than 2 weeks of age to fail to respond to indomethacin compared with infants less than 2 weeks of age who had a higher likelihood of responding to the drug. One may speculate that by delaying indomethacin administration, post-natal changes in prostaglandin metabolism in pulmonary and/or ductal tissue may occur that blunt the response to indomethacin, since developmental differences in response to indomethacin,[22,23] as well as to other stimuli have been well documented.[16,18,21]

Areas of potential concern with the use of systemic indomethacin in premature infants have mainly focused on two problems; the effects of inhibition of prostaglandin synthesis on renal function, and the potential for bleeding as a result of alterations in platelet physiology.

Prostaglandins are synthesized in the renal medulla and cortex [120] and have been shown to be important mediators of renal blood flow and its intra-renal distribution[120,129,130] as well as an active intermediary in regulation of the renin-angiotensin system.[131] Excretion of prostaglandin E in the urine following indomethacin administration declines when compared to quantities excreted before treatment, in a dose related fashion,[132] indicating that systemic use of indomethacin inhibits prostaglandin synthesis intra-renally. Therefore, systemic use of a prostaglandin synthetase inhibitor would be expected to show its effects in vascular beds that were mediated physiologically, at least in part, by prostaglandins.

Despite the effects of indomethacin on the renal vasculature, no permanent abnormalities in renal function were noted in this study after treatment with indomethacin. Six patients were, however, noted to have transient oliguria following the indomethacin dose, an effect which has been shown to be dose related, [124] and which has previously been reported in other studies. [25,109] This was probably due to constriction of the renal vascular bed from inhibition of endogenous renal prostaglandins resulting in a decrease in glomerular filtration. Azotemia was not recorded as might be expected to occur in such a situation. This finding has been reported by others, again in an apparent dose dependent relation.[97,109] The absence of azotemia in the present study may have been due either to sufficiently low doses of the drug that prevented severe compromise of renal blood flow, or may not have been seen because BUN/Creatinine determinations were not routinely measured in the immediate post-indomethacin period in a

standardized fashion but were obtained at various times after the drug was given.

A decrease in urine output may be a necessary effect in premature infants treated with indomethacin for a patent ductus arteriosus in order to have definitive evidence that the drug has been absorbed. Failure to obtain reliable absorption may contribute to the variability in response among patients. Use of parenteral forms of the drug may obviate this problem in the future [133] although controlled studies comparing the efficacy of IV vs. PO therapy have yet to be reported. Plasma indomethacin levels [134] may also become more widely available to better correlate drug levels with response.

Another complication of practical concern is that of bleeding which may occur from alteration in platelet function, a process dependent on prostaglandins. No serious bleeding diatheses were encountered in the patients treated with indomethacin in this study. One patient did have a transient episode of guaiac positive stools which spontaneously resolved and may have been related to the drug. In no other patients were any bleeding tendencies or hematologic abnormalities observed.

Indomethacin therefore appears to be a safe, and effective means of closing the patent ductus in the premature infant through inhibition of prostaglandin synthesis, and was not, in this study, associated with any major drug induced complications.

It must be remembered that indomethacin is a non-selective inhibitor of prostaglandin metabolism. It blocks the first step in the arachidonic acid cascade preventing further synthesis of both prostacyclin

and thromboxane metabolites.[55] This results in both theoretical and practical disadvantages, since alterations in biochemical pathways occurring on a systemic level therefore take place. The specific inhibition of only the prostacyclin arm of the cascade, which represents the vascular smooth muscle relaxants as well as the precursors of the prostaglandins, would enable more specific pharmacological intervention to occur in those tissues where the effect was actually wanted. While some preliminary work has been done in this area, it has been limited to in vitro stiuations.[56] Further delineation of pharmacological agents with this enzymatic specificity will enable more localized actions to occur with these compounds, and is an area of major concern for future research.

In summary, a patient population has been described which, despite certain common features, exhibits a wide variability in clinical and physiological status, course of disease and response to therapy. Many cases of a patent ductus arteriosus may go on to close spontaneously without specific intervention or may respond well to supportive medical management. The medical approach aims at symptomatic treatment of complications related to congestive heart failure and volume overload, and treatment of these symptoms with digitalis, diuretics, and fluid restriction.

Failure to note prompt response to the above therapy should probably be followed by an attempt to close the ductus with indomethacin as early as possible since delay may reduce the likelihood of response and allow pulmonary disease to progress. One would then be faced with

the subsequent alternative of an intra-thoracic procedure being carried out at higher risk due to the potentially unstable cardiopulmonary status of the patient before surgery.

The many variables that complicate the course and outcome of these infants still leave unresolved questions that bear directly on each phase of treatment. Variability in severity of pulmonary disease and resultant respirator dependence, impact of a patent ductus on the lung disease, degree of prematurity, potential for adequate caloric intake in the face of possible volume overloading, selection of patients, and timing of pharmacological and/or surgical intervention are some of the areas where conflicting reports have been published implicating success or failure in treatment of a symptomatic patent ductus arteriosus while controlling for some, but not all variables. While the vast majority of evidence implies few hazardous side effects and complications with the use of indomethacin as a treatment modality thus far, systemic application of a drug with effects in all tissues requires incontrovertible evidence that this is the case in populations studied carefully over an extended period of time. The efficacy of alternative treatment plans in light of the fact that there may be greater than a 40% spontaneous recovery rate from a symptomatic patent ductus arteriosus [127] must be investigated, as well as the relative morbidity and mortality from the lesion in populations treated either medically, pharmacologically, or surgically. While there is abundant justification both for the avoidance of surgery and for the assumption that indomethacin represents a safe, non-traumatic method for treatment of patent ductus arteriosus, a well controlled, prospective

multicentered study such as the twelve center co-operative study currently under way, may be the only approach towards resolving the dilemma regarding the best treatment for the patent ductus arteriosus.

REFERENCES

1. Burnard, ED: A murmur that may arise from the ductus arteriosus in the human baby. Proc. Roy. Soc. Med. 52:77-78, 1959.

2. Holmes, RL: Some features of the ductus arteriosus. J. Anat. Lond. 92:304-309, 1958.

3. Desligneus, S., and Larroche, JC: I. Ductus arteriosus: Anatomical and histological study of its development during the second half of gestation and its closure after birth. II. Histologic of a few cases of patent ductus arteriosus in infancy. Biol. Neonate 16:278, 1970.

4. Friedman, WF, Heyman, MA and Rudolph, AM: Commentary: New thoughts on an old problem. Patent ductus arteriosus in the premature infant. J. Pediatr 90:2,338-340, 1977.

5. Broccoli, F. and Carinci, P.: Histological and histochemical analysis of the obliteration processes of ductus arteriosus Botalli Acta Anat 85:69-83, 1973.

6. Fay FS, Cooke, PH: Guinea pig ductus arteriosus. II Irreversible closures after birth. Am. J. Physiol. 222:841-849, 1972.

7. Benajmin, DR, Wiegenstein, L: Necrosis of the ductus arteriosus in premature infarcts. Arch Pathol. 94:340-342, 1972.

8. Gittenberger-de Groot, HC: Persistent ductus arteriosus: Most probably a primary congenital malformation. Br. Heart J. 39:610-618, 1977.

9. Heymann, MA and Rudolph, AM: Control of the ductus arteriosus. Physiol. Rev. 55:62, 1975.

10. Rudolph, AM: The changes in the circulation after birth: Their importance in congenital heart disease. Circulation 41:343, 1970.

11. Rudolph, AM: Congenital Diseases of the Heart. Year Book Medical Publishers. 1974.

12. Dawes, GS, Mott, JC, Widdicombe, JG et al: Changes in lungs of new-born lamb. J. Physiol (London) 121:141, 1953.

13. Heymann, MH, Rudolph, AM, Nies, AS and Melmon, KL: Bradykinin production associated with oxygenation of the fetal lamb. Circ. Res. 25:521, 1969.

14. Melman, KL, Cline, MJ, Hughes, T. and Nies, AS: Kinins: Possible mediators of neonatal circulatory changes in man. J Clin Invest 47:1295-1302, 1968.

15. Hornblad, PY: Embryological observations of the ductus arteriosus in the guinea pig, rabbit, rat, and mouse: Studies on the closure of the ductus arteriosus IV. Acta Physiol Scand 76:49-57, 1969.

16. Oberhansli-Weiss, I, Heymann, MA, Rudolph, AM, Melmon, KL: The pattern and mechanisms of response to oxygen by the ductus arteriosus and pulmonary artery. Pediatr Res. 6:693-700, 1972.

17. McMurphy, DM, Heymann, MA, Rudolph, A, and Melmon, KL: Developmental changes in constriction of the ductus arteriosus. Responses to oxygen and vasactive agents in the isolated ductus arteriosus of the fetal lamb. Pediatr Res. 6:231, 1972.

18. Thibeault, DW, Clutario, B, Field, P: Arterial oxygen tension in premature infants. J Pediatr 69:449-51, 1966.

19. Neal, WA, Bessinger, FB, Hunt, CE and Lucas, RV: Patent ductus arteriosus complicating respiratory distress syndrome. J Pediatr 86:127, 1975.

20. Kitterman, JA, Edmunds, H, Jr., Gregory, GA, Heymann, MA, Tooley, WH, and Rudolph, AM: Patent ductus arteriosus in premature infants. Incidence relation to pulmonary disease and management. N Engl J Med 287:473, 1972.

21. Ikeda, M, Rubinstein, EH, and Sonnenschein, RR: Development of O_2 induced contractions in the ductus arteriosus of the guinea pig. Experientia 29:445, 1973.

22. Pace-Asciak, C. and Miller, D: Prostaglandins during development. I. Age-dependent activity profiles of prostaglandin 15-hydroxydehydrogenase and 13,14 reductase in lung tissue from late prenatal, early postnatal and adult rats. Prostaglandins 4:351, 1973.

23. Sharpe, GL, SuneLarsson, K and Thalmes, B: Studies on closure of the ductus arteriosus, XII. In utero effect of indomethacin and sodium salicylate in rats and rabbits. Prostaglandins 9:585, 1975.

24. Friedman, WF: Letter - NEJM 296:2,106, 1977.

25. Neal, WA, Kyle, JM, Mullett, MD: Failure of indomethacin therapy to induce closure of patent ductus arteriosus in premature infants with respiratory distress syndrome. J Peds 91:4, 621-23, 1977.

26. Kochs, JB: Letter NEJM, 296:2, 106, 1977.

27. McGrath, RL, Wolfer, RR, Simmons, MA, Nora, JJ: Letter, NEJM 296:2,106, 1977.

28. The Ductus Arteriosus. Proceedings of the Seventy-Fifth Ross Conference on Pediatric Research, Columbus, Ohio, Ross Laboratories, 1978.

29. Rudolph, AM and Heymann, MA: Medical treatment of the ductus arteriosus. Hospital Practice 57-65, 1977.

30. Assali, NS, Morris, JA, Smith, RW and Manson, WA: Studies on the ductus arteriosus circulations. Circ. Res. 13:478-489, 1963.

31. Kovalcik, V: The response of the isolated ductus arteriosus to oxygen and anoxia. J Physiol (Lond) 169:185-187, 1963.

32. Born, GVR, Dawes, GS, Mott, JC and Rennick, BR: The constriction of the ductus arteriosus caused by oxygen and asphyxia in newborn lambs. J Physiol (Lond) 132:304-342, 1956.

33. Fay, FS: Guinea pig ductus arteriosus. I. Cellular and metabolic basis for oxygen sensitivity. Am J Physiol 221:470, 1971.

34. Zapol, WM, Kolobous, T, Poppman, J and Pierce, JE: Responses of ductus arteriosus and pulmonary blood flow to blood oxygen tension in immersed lamb fetuses perfused through an artificial placenta. J Thoracic Cardiovascular Surg 61:891-903, 1971.

35. Kennedy, JA and Clark, SL: Observations on the physiological reactions of the ductus arteriosus. Amer J Physiol 136:140-147, 1942.

36. Clyman, RI and Rudolph, AM: Patent ductus arteriosus: A new light on an old problem. Pediatr Res 12:92-94, 1978.

37. Molnar, JJ, Mesel, E, Golinko, RJ, et al: Structure, histochemistry and physiology of ductus arteriosus in the dog. J Histochem Cytochem 10:667, 1962.

38. Aronson, S, Gemnser, G., Owman, CH and Sjoberg, NO: Innervation and contractile response of the human ductus arteriosus. Eur J Pharmacol 11:178, 1970.

39. Boreus, LO, Malmfors, T., McMurphy, DM, and Olson, L: Demonstration of adrenergic receptor function and innervation in the ductus arteriosus of the human fetus. Acta Physiol Scand 77:316, 1969.

40. McMurphy, DM, and Boreus, LO: Studies on the pharmacology of the perfused human fetal ductus arteriosus. Amer J Obstet. Gynec 109:937, 1971.

41. Smith, RW, Morris, JA, Assoli, NS: Effects of chemical mediators on the pulmonary and ductus arteriosus. Circulation in the fetal lamb. Amer J Obstet Gynec 89:252-260, 1964.

42. Ikeda, M: Adrenergic innervation of the ductus arteriosus of the fetal lamb. Experientia 26:525-526, 1970.

43. Kovalcik, V, Kriska, M., Dolezel, S: The problem of adrenergic innervation of the ductus arteriosus in the guinea pig fetus and its role in the mechanism of constriction. Physiologic Bohemoslovace, 18:401, 1969.

44. Goodman, LS, and Gilman, A.: The Pharmacological Basis of Therapeutics Ed. 5, N.Y., Macmillan Pub. Co., 1975.

45. Editorial - Prostaglandins and the ductus arteriosus. Lancet 2: 7990, p 837, 1976.

46. Coceani, F and Olley, PM: The response of the ductus arteriosus to prostaglandins. Can J Physiol Pharmacol 51:220, 1973.

47. Shiling, MB and Elliott, RB: The effects of prostaglandins, prostaglandin inhibitors and oxygen on the closure of the ductus arteriosus, pulmonary arteries and umbilical vessels in vitro. Prostaglandins 8:187, 1974.

48. Elliott, RB and Starling, MB: The effect of prostaglandin $F2\alpha$ in the closure of the ductus arteriosus. Prostaglandins 2:399, 1972.

49. Sharpe, GL and Larsson, KS: Studies on closure of the ductus arteriosus X. In vivo effect of prostaglandins. Prostaglandins 9:704, 1975.

50. Coceani, F and Wolfe, LS: On the action of PGE_1 and prostaglandins from brain on the isolated rat stomach. Can J Physiol Pharmacol 44:933-950, 1966.

51. Elliott, RB, Starling, MB and Neutze, JM: Medical manipulation of the ductus arteriosus. Lancet 1:140, 1975.

52. Heymann, MA, Rudolph, AM: Dilatation of the ductus arteriosus in infants with pulmonic atresia. Pediatr Res 10:313, 1976.

53. Olley, PM: Nonsurgical palliation of congenital heart malformations. N Engl Jrl Med 292:1292-1294, 1975.

54. Olley, PM, Coceani, F, Bodach, E: E-type prostaglandins: A ew emergency therapy for certain cyanotic congenital heart malformations. Circulation 53:728-731, 1976.

55. Dusting, GJ, Moncade, S. and Vane, JR: Prostaglandins, their intermediates and precursors: Cardiovascular actions and regulatory roles in normal and abnormal circulatory systems. Prog. Cardiov. Dise. 21:6, 405-430, 1979.

56. Moncada, S and Vane, JR: Arachadonic acid metabolites and the interactions between platelets and blood vessel walls. N Engl Jrl Med 300:20, 1142-1148, 1979.

57. Moncada, S and Vane, JR: Unstable metabolites of arachiadonic acid and their role in haemostasis and thrombosis. Br Med Bull 34:129-135, 1978.

58. Armstrong, JM, Lattimer, N, Moncada, S et al: Comparison of the vasodepressor effects of prostacyclin and 6-oxo-prostaglandin Fiα with those of prostaglandin E2 in rats and rabbits. Br J Pharmacol 62:125-130, 1978.

59. Needleman, P, Minkes, M, Raz, A: Thromboxanes: Selective biosynthesis and distinct biological properties. Science 193:163, 1976.

60. Flower, RJ: Drugs which inhibit PG biosynthesis. Eur J Pharmacol Rev 26:33, 1974.

61. Collins, G, Outerbridge, E, Manker, MS, Horrobin, DF: Chloroquine as prostaglandin antagonist in treatment of patent ductus arteriosus. Lancet 2:79, p 810, 1976.

62. Heymann, MA and Rudolph, AM: Effects of acetylsalicylic acid on the ductus arteriosus and circulation in fetal lambs in utero. Circ Res 38:418, 1976.

63. Sharpe, GL, Thalme, B, and Larsson, KS: Studies on closure of the ductus arteriosus. XI. Ductual closure in utero by a prostaglandin synthetase inhibitor. Prostaglandins 8:363, 1974.

64. Levin, DL, Fixler, DE, Morriss, FC, Tyson, J: Morphologic analysis of the pulmonary vascular bed in infants exposed in utero to prostaglandin synthetase inhibitors. J Pediatr 92:3, 478-83, 1978.

65. Parks, BR, Rawson, JF, and Douglas, BH: In utero death as a possible consequence of prenatal administration of indomethacin. Pediatr Res. 11:No 4, 419, 1977.

66. Turner, G, and Collins, E: Fetal effects of regular salicylate ingestion in pregnancy. Lancet 2:338, 1975.

67. Coceani, F, Olley, PM and Bodach, E: Lamb dutus arteriosus: Effect of prostaglandin synthesis inhibitors on the muscle tone and the response to prostaglandin E_2. Prostaglandin 9:299, 1975.

68. Kirkpatrick, SE, Printz, MP and Friedman, WF: Prostaglandins (PG's) and the fetal ductus arteriosus (PDA). Pediatr Res 11:No 4 (abstract) 1977.

69. Olley, PM, Bodach, E, Heaton, J, Coceani, F: Further evidence implicating E type prostaglandins in the patency of the lamb ductus arteriosus. Eu J Pharmacol. 34:247, 1975.

70. Cooper, LZ, Ziring, PR, Ockerse, AB, Feders, BA, Kieley, B, Krugman, S: Rubella: Clinical manifestation and management. Amer J Dis Child, 118:18, 1969.

71. Esterly, JR and Oppenheimer, EH: Pathological lesions due to congenital rubella. Arch Path 87:380, 1969.

72. Campbell, PE: Vascular abnormalities following maternal rubella. Brit Heart J 27:134, 1965.

73. Cascos, AS and Sagredo, JM: Genetics of patent ductus arteriosus. Basic Res Cardiol 70:4, 456-466, 1975.

74. Patterson, DF, Pyle, RL, Buchanan, JW, Trantvetter, E and Abt, DA: Hereditary patent ductus arteriosus and its sequelae in the dog. Circul Res 29:1, 1971.

75. Penzaloza, D, Arias-Stella, J, Sime, F, et al: The heart and pulmonary circulation in children at high altitudes: Physiological, anatomical and clinical observations. Pediatrics 34:568-582, 1964.

76. Alzamorea-Castro, V, Battilana, G, Abugattas, R and Sialer, S: Patent ductus arteriosus and high altidue. Am J Cardiol 5:761-763, 1960.

77. Blanco, CE, Siassi, B. and Cabal, LA: Persistent patency of the ductus arteriosus in premature newborn infants. Am J Cardiol (abstr) 31:120, 1973.

78. Danilowicz, D, Rudolph, AM, Hoffman, JIE: Delayed closure of the ductus arteriosus in premature infants. Pediatrics 37:74-78,1966.

79. Thibeault, D, Emmanouilides, GC, Nelson, RJ, Rosengart, R, Oh, W, Lachman, R: Patent ductus arteriosus in infants less than 30 weeks gestation: Indications for surgery (abst). Pediatric Res. 8:355, 1974.

80. Friedman, WF: The intrinsic physiologic properties of the developing heart. Prog Cardiovasc Dis 15:87-111, 1972.

81. Sonnenblick, EH, Spiro, D and Spotnitz, H: Ultrastructural basis of Starling's law of the heart. Amer Heart J 68:336, 1964.

82. Romero, R, Covell, J, Friedman, WF: A comparison of pressure-volume relations of the fetal, newborn, and adult heart. Am J Physiol 222:1285-1290, 1972.

83. Klopfenstein, HS and Rudolph, AM: Postnatal changes in the circulation and responses to volume loading in sheep. Circ Res 42:6,839-845, 1978.

84. Lebowitz, EA, Novick, JS, Rudolph, AM: Development of myocardial sympathetic innervation in the fetal lamb. Pediatr Res 6:887-893, 1972.

85. Krovetz, I, and Kattwinkel, J: Commentary on patent ductus arteriosus complicating the respiratory distress syndrome. J Pediatr 90:2, 262-263, 1977.

86. Stevenson, JG: Fluid administration in the association of patent ductus arteriosus complicating respiratory distress syndrome. J Pediatr 90:257, 1977.

87. Warburton, D, Bell, EF, Stonestreet, BS, Oh, W: Effects of high and low volume fluid administration in low birth weight infants: A prospective echocardiographic study. Ped Res 13:4, 353, 1979.

88. Gersony, W: Commentary: Patent ductus arteriosus and the respiratory distress syndrome - a perspective. J Pediatr 91:4, 624-625, 1977.

89. Nadas, A: Patent ductus arteriosus revisited. NEJM 295:10, 563, 1976.

90. Heymann, A: Patent ductus arteriosus, in Moss, AJ, Adams, FH, Emmanouilides, GC (eds): Heart Disease in Infants, Children and Adolescents. Baltimore, Williams and Wilkins Co. 1977, p 168.

91. Juratsch, CE, Emmanouilides, GC, Thibeault, D, Bonzlen, B, Jingo, LA, Laks, MM, Criley, JM: Main pulmonary artery distention: Potential mechanism for sustained pulmonary hypertension in the newborn. Circ 56(suppl 3):73, 1977.

92. Johson, DS, Rogers, JH, Null, DM, deLermos, RA: The physiologic consequences of the ductus arteriosus in the extremely immature newborn. Clin Res 26:6, 826, 1978.

93. Thibeault, DW, Emmanouilides, GC, Nelson, RJ, Lachman, RS, Rosengart, RM, Oh, W: Patent ductus arteriosus complicating the respiratory distress syndrome in preterm infants. J Pediatr 86:1, 120-126, 1975.

94. Talner, NS in Cardiovascular Clinics Vol 4, No 3, 1972., Pediatric Cardiology. A.N. Brest, Ed. FA Davis Co., Phila, Penna.

95. Touloukian, RJ: Neonatal necrotizing enterocolitis: An update on etiology, diagnosis and treatment. Surgical Clinics of North American, Vol 56:No. 2, 1976.

96. Mitchell, SC, Korones, SB, Berendes, HW: Congenital heart disease in 56,109 births: Incidence and natural history. Circulation 63: 323-332, 1971.

97. Friedman, WF, Hirschklau, MJ, Printz, MP, Pitlick, PT, Kirkpatric, SE: Pharmacologic closure of patent ductus arteriosus in the premature infant. NEJM 295:10, 526, 1976.

98. Cotton, RB, Stahlman, MT, Kovac, I, Catterton, WZ: Medical management of small preterm infants with symptomatic patent ductus arteriosus. J Pediatr 92:3, 467-473, 1978.

99. Rudolph, AM Ed Pediatrics Appleton Cent Crofts 1977.

100. Allen, HD, Sahn, DJ, Goldberg, SJ: New serial contrast technique for assessment of left to right shunting patent ductus arteriosus in the neonate. Am J Cardiol 41:288-294, 1978.

101. Baylen, BG, Meyer, RA, Kaplan, S, et al: The critically ill premature infant with patent ductus arteriosus and pulmonary disease: an echocardiographic assessment. J Pediatr 86:42-432, 1975.

102. Wesenberg, RL, Wax, RE and Zachman, RD: Varying roentgenographic patterns of patent ductus arteriosus in the newborn. Am J Roentgenol 114:340, 1972.

103. Silverman, NJ, Lewis, AB, Heyman, MA et al: Echocardiographic assessment of ductus arteriosus shunts in premature infants. Circulation 50:821-825, 1974.

104. Hirschklaus, MJ, DiSessa, TG, Higgins, CB and Friedman, WF: Echocardiographic diagnosis: Pitfalls in the premature infant with a large patent ductus arteriosus. J Pediatr 92:3, 474-477, 1978.

105. Baylen, B, Meyer, RA, Kaplan, S: Echocardiographic assessment of patent ductus arteriosus in prematures with respiratory distress. Pediatric Res 8:347, 1974 (abst)

106. Silverman, NH, Lewis, AB, Heyman, MA, Rudolph, AM: Echocardiography with patent ductus arteriosus in premature infants. Pediatr Res 8:355, 1974. (abst)

107. Allen HD, Goldberg, SJ, Sahn, DJ, et al: Suprasternal notch echocardiography assessment of its clinical utility in pediatric cardiology. Circ 55:605-612, 1977.

108. Kitterman, JA, Phibbs, RH, Tooley, WH: Catheterization of umbilical vessels in the newborn infant. Pediatr Clin North Am 17:895-912, 1970.

109. Heymann, MA, Rudolph, AM, Silverman, WH: Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. NEJM 295:530, 1976.

110. Stewart, AR, Moriarty, R, Ulan, OD, Finer, N: Medical management of patent ductus arteriosus in hyaline membrane disease (abst). Pediatr Res 11:No 4, 401, 1977.

111. Edmunds, LH, Gregory, GA, Heymann, MA, Kitterman, JA, Rudolph, AM Tooley, SH: Surgical closure of the ductus arteriosus in premature infants. Circulation 48:856, 1973.

112. Rittenhouse, EA, Doty, DB, Lauer, RM, Ehrenhaft, JL: Patent ductus arteriosus in premature infants. Indications for surgery. J Thorac Cardiovas Surg 71:187, 1976.

113. Lees, MH: Commentary: Patent ductus arteriosus in premature infants - a diagnostic and therapeutic dilemma. J Pedatr 86:1, 132-134, 1975.

114. Murphy, DA, Onterbridge, E, Stern, L, Kasn, GM, Jegier, W. and Rosales, J: Management of premature infants with patent ductus arteriosus. J Thorac Cardiovasc Surg 67:221, 1974.

115. Jacobs, JC: Sudden death in arthritic children receiving large doses of indomethacin. JAMA 199:932-934, 1967.

116. Friedman, Z, Whitman, V., Maizels, M, Berman, W, Marks, K, Vessel, E: Indomethacin disposition and indomethacin induced platelet dysfunction in premature infants. J Clin Pharm May-June 1978, pp 272-279.

117. Koch-Weser J, Sellers, EM: Binding of drugs to serum albumin. NEJM 294:311-316, 1976.

118. Talner, N.S.: Personal communication.

119. Rasmussen, LF, Ahlfors, CE and Wennenberg, RP: Displacement of bilirubin from albumin by indomethacin. J Clin Pharm, 1978, 477-481.

120. McGiff, JC, Cranshaw, K, Itskovitz, HD: Prostaglandin and renal function. Fed Proc 33:39-47, 1974.

121. Millard, RW, Baig, H, Vatner, S: Renal vascular protection by prostaglandin during hypoxemia in unanesthetized fetal lamb. Pediatr Res 11:No 4, 395, 1977 (abst).

122. Harinck, E, Van Ertbraggen, I, Senders, RC, Monlaert, AJ: Problems with indomethacin for ductus closure. Lancet 2:8031, p 245, 1977.

123. Merritt, TA, White CL, Hirschklan, MJ, Friedman, WF, Gluck, L: Infant follow up with indomethacin closure of patent ductus arteriosus. Pediatr Res 11:No 4, 395, 1977.

124. Winther, J, Printz, MP, Mendoza, SA, Kirkpatrick, SE and Friedman, WF: The influence of indomethacin on neonatal renal function. Pediatr Res. 11:No. 4 (abstract) 1977.

125. Nestrand, R, Hill, D., Arrington, R., et al: A double blind controlled study on the efficacy of indomethacin in closure of the patent ductus arteriosus in premature infants. Ped Res 13:4, 349, 1979.

126. Truscone, NJ, Cepida, E, Green, E. et al: Management of patent ductus arteriosus in premies. weighing less than 1500 grams. Ped Res 11:4, 391, 1978.

127. Yanagi, R, Aziz, K, Hunt, C: Efficacy of indomethacin for symptomatic patent ductus arteriosus: A double blind control study. Ped Res 13:4, 354, 1979.

128. Yanagi, R, Wilson, A, Fletcher, MA, et al: Efficacy of indocin for symptomatic patent ductus arteriosus: A double blind controlled study. Ped Res 12:4, 392, 1978.

129. Lonigro, AJ, Itskovitz, HD, Cranshaw, K and McGiff, JC: Dependency of renal blood flow on prostaglandin synthesis in the dog. Circ Res 32:712, 1973.

130. Herbaczynska-Cedro, K and Vane, JR: Contribution of intrarenal generation of prostaglandin to autoregulation of renal blood flow in the dog. Circ Res 33:428, 1973.

131. Frolich, JC, Hollifield, JW, Dormois, JC et al: Suppression of plasma renin activity by indomethacin in man. Circ Res 39:447, 1976.

132. Friedman, Z, Demers, LM et al: Urinary excretion of prostaglandin E following the administration of furosemide and indomethacin to sick low birthweight infants. Ped Res 12:4, 381, 1978.

133. Yeh, TF, Thalj, A, Luken, J, Raval, D, Carr, I, Pildes, RS: Intravenous indocin therapy in premature infants with patent ductus arteriosus: A double-blind control study. Ped Res 13:4, 354, 1979.

134. Alpert, BS, Lewins, MJ, Rowland, DW et al: Plasma indomethacin levels in newborns with patent ductus arteriosus. Ped Res 13:4, 339, 1979.