The ductus arteriosus in the preterm infant: Histologic and clinical observations

In order to elucidate some of the unexplained phenomena in prolonged patency of the ductus arteriosus in preterm infants, the histology of the ductus was studied in 27 cases. Some of the infants had been treated with indomethacin. Four morphologic maturation stages are distinguished. There was no strict relation between gestational age or birth weight and histologic maturation. Therefore, one cannot predict whether a ductus is likely to be mature at the time of birth. In all infants with clinically diagnosed prolonged patency of the ductus beyond the first week, the immature maturation stage or the permanent patent type was observed. In both stages, reopening after initial closure with indomethacin occurred.

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PROLONGED PATENCY of the ductus arteriosus in preterm infants with a large left-to-right shunt often leads to cardiopulmonary distress. Its increased incidence over the last few years[1] is probably due to improved neonatal intensive care. A satisfactory explanation of the cause of delayed ductal closure in preterm infants has not been found. Sooner or later spontaneous closure is seen in most infants. Immediate closure of the ductus after birth in very immature infants may also occur.[1-2]

In recent years pharmacologic closure with indomethacin has been attempted,[3-8] and closure may be obtained in this way. However, both lack of response and reopening after initial contraction with indomethacin have been observed.[4-8]

To contribute to a better understanding of the above mentioned problems, we did a histologic study of the ductus tissue of preterm human infants.

SUBJECTS AND METHODS†

The ducts of 27 preterm infants, with gestational ages ranging from 24 to 37 weeks and varying in age from 10 hours to 5½ months, were studied. The ducts, with the adjacent parts of the aorta and pulmonary artery, were removed at autopsy. The material was fixed in alcohol/glycerine and prepared routinely for histologic examination. All specimens were completely serially sectioned and the sections stained alternately with hematoxylin-eosin, azan, resorcin fuchsin, and van Gieson elastic tissue stain.

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For comparison, we also studied 15 ducts from fetuses with a gestational age of 16 to 23 weeks, who either were born dead or did not live longer than one hour. Furthermore, 40 ducts from term infants ranging in age from 0 hours to several years, were investigated. Some of the results of this last group have been described previously.[9, 10] These latter studies indicated that in case of permanent patency of the ductus, also referred to as persistent patency, there is a primary anatomic defect of the ductus.

The histologic findings in the preterm infants were related to clinical data, birth weight, asphyxia at birth, incidence of respiratory distress, use of assisted ventilation, prolonged patency of the ductus, and cause of death. All infants had been admitted to a neonatal intensive care unit. The clinical recognition of patency of the ductus arteriosus during the first week of life was sometimes very difficult. It was often impossible to separate those infants

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†Tabulated clinical data available on special request.

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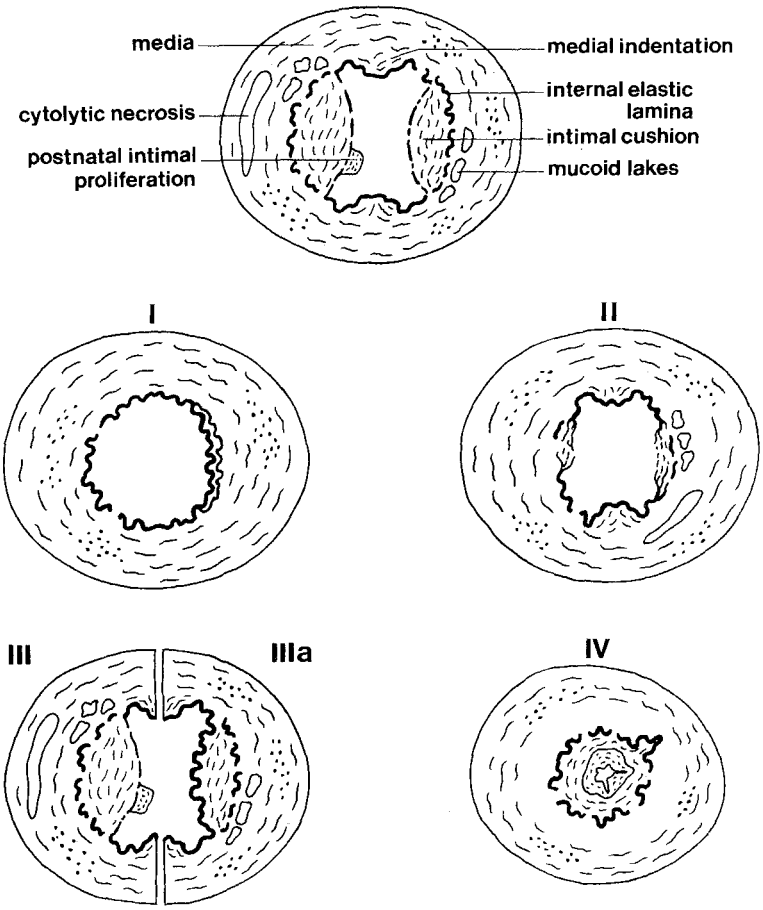

Fig. 1. Schematic representation of the four maturation stages. Stage IIIa indicates the structure of a ductus with permanent (persistent) patency.

who had pulmonary problems alone from those with cardiopulmonary distress.

RESULTS

Histologic maturation stages. Based on our own observations on the histology of the ductus in the fetal and neonatal periods,[10] and on literature data,[11-14] four morphologic maturation stages are distinguished (Fig. 1):

Stage I (Figs. 1 and 2) 5 cases. The human ductus arteriosus of a 4- to 5-month-old fetus resembles a muscular artery. It is wedged between the aorta and the pulmonary artery, both having an elastic type of vessel wall. The internal elastic lamina may either be single or locally duplicated. Small interruptions are frequently encountered. The intima consists of a very thin layer with endothelial cells bordering the lumen.

Stage II (Figs. 1 and 3) 5 cases. Local formation of small intimal thickenings or cushions is seen in this stage. The elastic muscular cushions protruding into the lumen of the ductus are real structures and should not be confused with the medial indentations described by Hörnblad,[15] which are the result of postnatal ductal constriction and modify the internal part of the media. The medial indentations constitute the main protrusions seen in the ductal lumen of most animals and are also present in the human ductus. However, in the latter they are less conspicuous, because of the intimal cushions partly overlying them.

Stage III (Figs. 1 and 4) 9 cases. This stage is characterized by a ductal wall showing all features attributed to normal anatomic closure. Stage III is encountered in almost every ductus from a term infant. It differs from Stage II in having more extensive and pronounced intimal cushions. If functional closure takes place during the first few hours to days of life, mucoid lakes and cytolytic necrosis may develop in the muscular media. The mucoid lakes develop from the large amount of mucoid substance normally present in the ductal wall. With the stagnation of flow and thickening of the wall during functional closure, the nutrition of the middle part of the ductal wall becomes

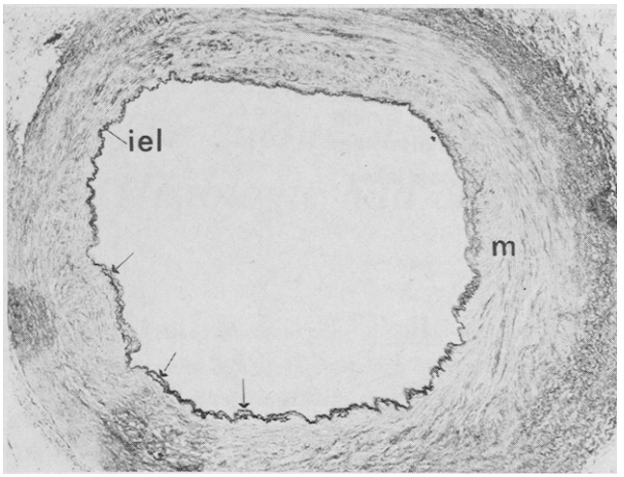

Fig. 2. Transverse section of a Stage I ductus arteriosus of a 27-week preterm infant who lived 28 days. The internal elastic lamina *(iel)* lie subendothelial. In several places there is duplication (→) of the iel. The media *(m)* contains no elastic lamellae. (Van Gieson elastic tissue stain; 31×.)

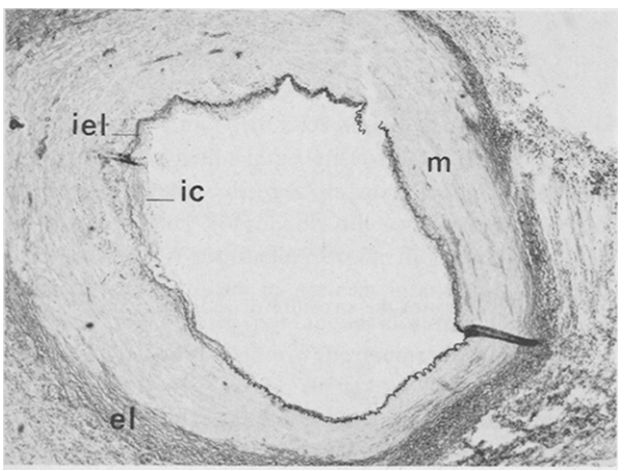

Fig. 3. Transverse section of a Stage II ductus arteriosus of a 30-week preterm infant who lived 31 hours. Small intimal cushions *(ic)* protrude into the lemen. The internal elastic lamina *(iel)* lies on the borderline between ic and media *(m)*. The elastic lamellae *(el)* of the aorta are still visible in the outer part of the media. (Van Gieson elastic tissue stain; 26×.)

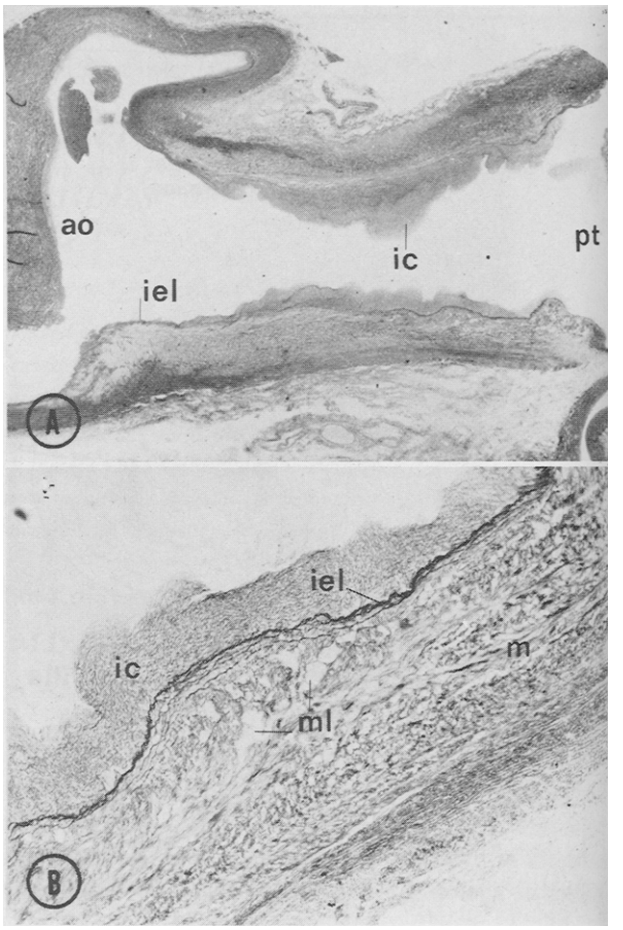

Fig. 4. *A*, Sagittal section of the ductus arteriosus of a 32-week premature infant who lived 12 hours. The ductus is seen with its connection to the aorta *(ao)* and pulmonary trunk *(pt)*. The elastic lamellae of the ao and pt merge for two-thirds into the outer part of the media of the ductus, while the inner third forms the internal elastic lamina *(iel)*. Marked intimal cushions *(ic)* protrude into the lumen. *B*, Detail of *A*. The intimal cushions *(ic)* are thick and contain fine elastic fibers. The internal elastic lamina *(iel)* is exceptional in that it is not fragmented. The media *(m)* shows several mucoid lakes *(ml)*. (Van Gieson elastic tissue stain; *A*, 8×; *B*, 35×.)

insufficient. A very typical kind of necrosis, with loss of nuclei and absent cellular infiltration, then develops (so-called cytolytic necrosis).

Stage IIIa (Figs. 1 and 5) 3 cases. While studying the histology of prolonged patency of the ductus in the term neonate, it was found that in infants with permanent (persistent) patency, a subendothelial elastic lamina borders the lumen. This lamina could either by the internal elastic lamina or an additional lamina on top of the intimal cushions.[9] This constitutes a primary anatomic defect of the ductus. Buchanan[16] studied the histology of the ductus in dogs with hereditary persistent ductus arteriosus. Concurrent with a reduction of the smooth muscle fibers, an increase in the amount of aortic-like elastic tissue is seen in these animals. An increase of elastic lamellae in the media of the ductal wall ("aortification") is seen in only a minority of the human ducts with permanent patency; usually a normal amount of smooth muscle is present, and the only marked histologic abnormality is the subendothelial elastic lamina.[9]

Stage IV (Figs. 1 and 6) 5 cases. With definitive sealing of the ductal lumen during anatomic closure, the intimal cushions fuse. At sites where a lumen persists, it is filled with new loose fibrous tissue devoid of elastic fibers,

so-called postnatal intimal proliferation. The central core of the ductus shrinks considerably, and finally a ligament remains.

Gestational age and histologic maturation. A strict relation between ductal maturation and gestational age or age from birth could not be demonstrated. Whereas small intimal cushions typical for Stage II were observed as early as the seventeenth week of gestation, cushion formation could remain absent (Stage I) up to 36 weeks of gestation, as in a somewhat exceptional infant having a very low birth weight. Complete anatomic closure occurred in an infant of 27 weeks' gestation (Stage IV), whereas another infant of the same gestational age and similar age from birth had a widely patent ductus without any signs of anatomic closure (Stage I).

One case was exceptional in that almost complete anatomic closure of the pulmonary end of the ductus (Stage IV) was present 29 hours after birth, whereas the aortic end was still patent. Here at several sites a subendothelial elastic lamina showed on top of the initimal cushions a feature characteristic for a persistent type of ductus arteriosus (Stage IIIa). This wall structure, typical for cases with permanent patency of the ductus, was also seen in another three infants.

A relation between the histologic maturation stages and the incidence of asphyxia at birth, respiratory distress, use of assisted ventilation, and postmortem findings was not observed.

There was a direct relation between the clinical diagnosis of prolonged patency of the ductus and its morphologic state. When the ductus was functionally closed, the maturation stages proved either to be II, III, or IV. If the ducts were functionally still patent at the time of death, either Stage I or IIIa was seen.

Indomethacin had been administered to three infants. In one it was given on the eighth day, inducing a slight constriction of the ductus, which closed completely by the twenty-third day; five and a half months later the child died, and postmortem examination showed an anatomically closed ductus. In a second infant indomethacin had been given on the thirteenth to fourteenth day, resulting in a functionally closed ductus. Two days before death, however, the ductus reopened. Histologic observation showed a widely patent ductus in Stage I; no mucoid lakes or cytolytic necrosis developed during functional closure. A third infant received indomethacin on the sixteenth day, which caused some constriction of the ductus but not complete functional closure. Histologically the ductus was still patent with a very small lumen. No anatomic sealing was seen and the ductus had the structure of the persistent type, Stage IIIa.

In some of the ducts hemorrhages and necrosis of the ductal wall were seen, but were unrelated to the clinical data.

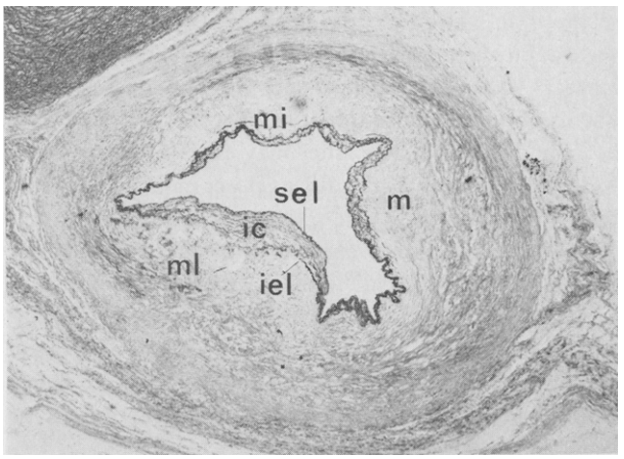

Fig. 5. Transverse section of a Stage IIIa ductus arteriosus of a 29-week preterm infant who lived 20 days, and received indomethacin on the sixteenth day. Typical for the persistent wall structure is the subendothelial elastic lamina *(sel)* on top of the intimal cushions *(ic)*. The internal elastic lamina *(iel)* underneath the cushion is fragmented. There are marked medial indentations *(mi)* which are the result of contraction of the ductus after birth. In the media *(m)* a mucoid lake *(ml)* is seen. (Van Gieson elastic tissue stain; 23×.)

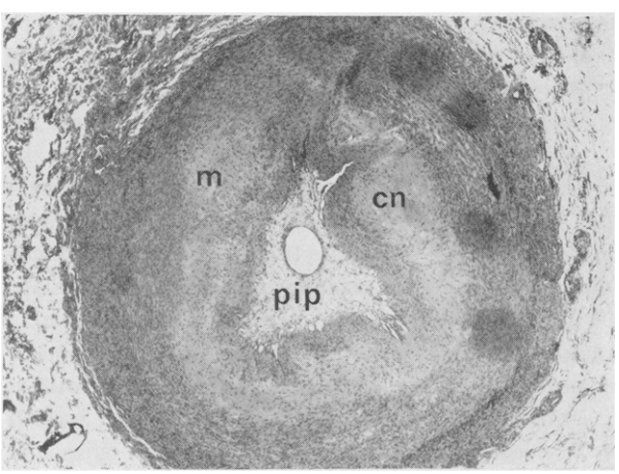

Fig. 6. Transverse section of a Stage IV ductus of a 33-week preterm infant who lived 35 days. The lumen is almost closed by postnatal intimal proliferation *(pip)*. The inner third of the media *(m)* shows a broad zone of cytolytic necrosis *(cn)*. (Hematoxylin-eosin tissue stain; 27×.)

DISCUSSION

There is an inverse relation between birth weight or gestational age and the incidence of prolonged patency of the ductus arteriosus.[1] Therefore, one might expect a direct relation between gestational age or birth weight and histologic maturation of the ductus arteriosus. Such a

relationship was only partly demonstrated. The maturity stage of the ductus in a preterm infant with gestational age 32 to 33 weeks can still be a very early one, whereas the ductus of an immature infant of 27 weeks' gestation can be fully developed. The latter may explain why in some very immature infants the ductus closes immediately after birth.[1, 2]

General conclusions regarding the relation between histologic and clinical findings should be critically appraised because of our limited material, consisting only of deceased infants. For instance, an incidence of approximately 10% for permanent patent ductus is seen, a figure which certainly does not apply to preterm infants in general.

Cases with a clinically patent ductus beyond one week had either a very immature ductus (Stage I), regardless of their gestational age, or a ductus histologically compatible with permanent (persistent) patency (Stage IIIa). In these two stages, anatomic sealing did not take place and reopening of the ductus was seen after initial closure with indomethacin. The thick elastic lamina bordering the lumen, characteristic of both stages, might play a role in inhibiting anatomic closure.

Reopening of the ductus after indomethacin may be explained on the basis of our histologic findings.[4-8] The variation in incidence of reopening or nonreactivity reported from the various centers might be based on variation of the type of patients treated, and may be directly related to the age after birth on which indomethacin treatment is started. This hypothesis was also suggested by McGrath et al.[8] If indomethacin is administered soon after birth, patients with Stage II or even Stage III ducts may be included, and these are capable of anatomic sealing, particularly after initial constriction by indomethacin. If treatment is started later after birth, as described by Neal et al,[4] some infants born with Stage II or III ducts may have selected themselves out by spontaneous closure, leaving a group of older patients with relatively more examples of very immature or even persistent types of ducts and, consequently, less response to indomethacin. A marked relation between response to indomethacin and age after birth can also be derived from data given by McCarthy et al.[6]

If medical closure is not attempted, the immature ductus most probably will slowly mature and eventually close spontaneously after several weeks to months, which is known to occur sometimes in the preterm infant.[17] Ducts with a type of wall typical for permanent (persistent) patency most probably will never close spontaneously, as is seen in the term infant.[9] The persistent ductus is capable of constricting with indomethacin and relaxes after administration of prostaglandin E_1.[18] Therefore, the mechanism which underlies the effect of clinically administered prostaglandin$_1$ and its inhibitors does not seem to be greatly disturbed in this type of ductus. This undermines the hypothesis of McCarthy et al,[6] suggesting that the number of adrenergic fibers in the media diminishes in the later stages of ductal development, causing the insensitivity to indomethacin. In ducts with permanent patency, no adrenergic fibers are seen in the media.[19] However, we cannot extrapolate findings from this aberrant type of ductus to the later stages of ductal development in general.

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