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Anatomical closure of the ductus arteriosus: a study in 35 specimens*

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INTRODUCTION

The obliteration of the ductus arteriosus has often been investigated in the past, and many hypotheses have been proposed to account for its closure. Histological studies have been based on animal material (e.g. Shaeffer, 1914; Sciacca & Condorelli, 1960; Hoefsmit, 1967; Hornblad, 1969; Mato, Aikawa & Uchiyama, 1971; Broccoli & Carinci, 1973) as well as on human (Jager & Wollenman, 1942; Danesino, Reynolds & Rehman, 1955; Bakker, 1962; Hoffman, 1964; Desligneres & Larroche, 1970 and Gittenberger-de-Groot, 1977). There is general agreement that the normal human ductus is closed by the end of the first year, and that patency after one year should be considered abnormal (Gerard, 1900; Scammon & Norris, 1918; Christie, 1930; Edwards, 1953).

As early as 1852, Rokitansky suggested that closure of the ductus resulted from direct adhesion and fusion of its walls without the mediation of thrombosis. Strassman (1894), later supported by Fay & Travill (1967), reported the presence of a 'valve' which effected immediate closure of the ductus. Although such 'valves' certainly occur in some animals, Cassels (1973) pointed out that they were unusual in man.

Most authors are of the opinion that the ductus arteriosus goes through an active morphological process characterized by an abundance of connective tissue and metachromatic ground substance beginning well before the beginning of autonomous life (Jager & Wollenman, 1942; Danesino *et al.* 1955; Jones, Barrow & Wheat, 1969; Desligneres & Larroche, 1970; Broccoli & Carinci, 1973). However, there are differing opinions regarding the precise nature of anatomical obliteration. Because of this, we have reviewed the histology of the persistent and closing ductus in 35 human specimens.

MATERIALS AND METHODS

Thirty five segments of human aortic arches with ductus arteriosus and portions of the pulmonary artery were resected from autopsy infant specimens of both sexes and studied histologically. These included seven arches from anatomically normal hearts, twelve associatied with coarctation or tubular hypoplasia and sixteen from hearts with other congenital malformations (Table 1). If a 1 mm probe could be inserted from the pulmonary artery to the aorta, the ductus was considered patent. The specimens ranged in age from newborn to 2¼ years.

The removed segments were sectioned either parallel to the longitudinal axis of

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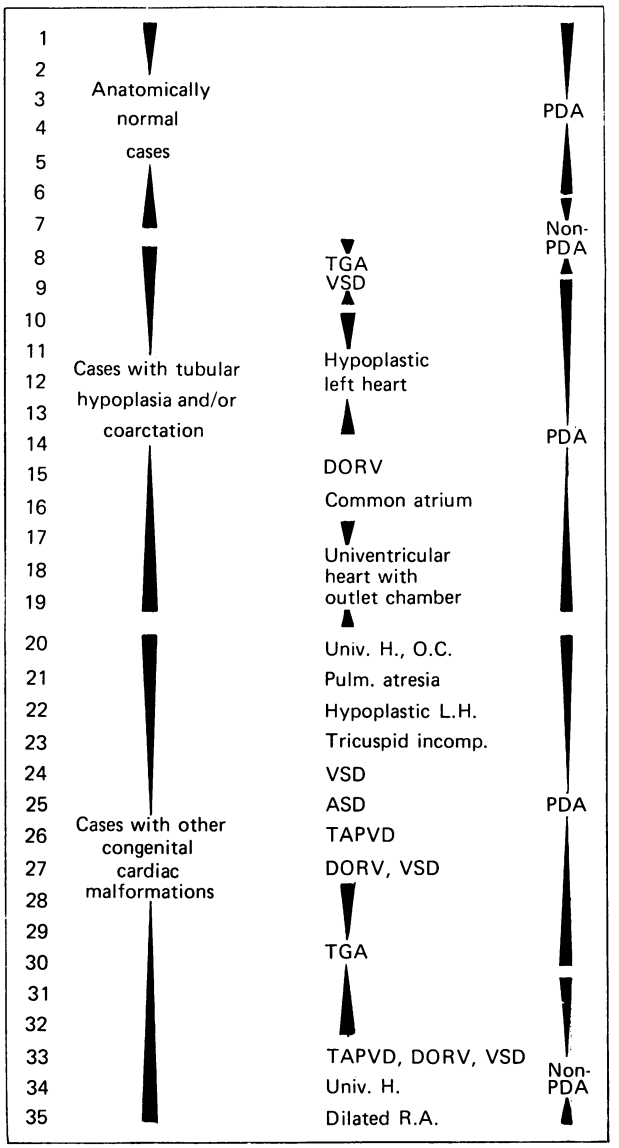
Table 1

Cases studied showing congenital malformations if present.



ASD	atrial septal defect
incomp.	incompetence
L.H.	left heart
O.C.	outlet chamber
Pulm.	pulmonary
R.A.	right atrium
TAPVD	total anomalous pulmonary drainage
Univ. H.	univentricular heart
DORV	double outlet right ventricle
PDA	patent ductus arteriosus
TGA	discordant ventriculo-arterial connexion
VSD	ventricular septal defect

the aortic arch, or in the sagittal plane of the ductus, or transversely. Serial sections were made and each twenty fifth section was mounted and stained with the modified Masson's trichrome technique (Smith, Ho & Anderson, 1977). Additional sections were stained in haematoxylin and eosin or Verhoeff's Van Gieson after studying the initial series.

RESULTS

Since there was an overall similarity in the structure of the normal ductus specimens and those associated with congenital heart anomalies, the histology of all 35 specimens is presented.

Overall histology

In general, the wall of the ductus arteriosus displayed an intima, a media of variable thickness, and an adventitia. An internal elastic membrane was present between intima and media (Fig. 1). This membrane was a wavy sheath and was rarely complete.

The adventitia was a poorly defined layer of fibrous tissue containing vasa vasorum and nerve fibres. It was not delimited from the external portion of the media by an external elastic membrane.

The media was composed mainly of loosely arranged smooth muscle fibres in a connective tissue matrix containing very fine, wavy elastic fibres. The muscle fibres in the outer third of the media were arranged spirally, and were penetrated by small groups of longitudinal fibres. The inner two thirds tended to have oblique-to-longitudinal fibres, depending on the state of contraction of the vessel. The more contracted the vessel, the more longitudinal these fibres became. Again, longitudinal bundles could be seen penetrating this inner media.

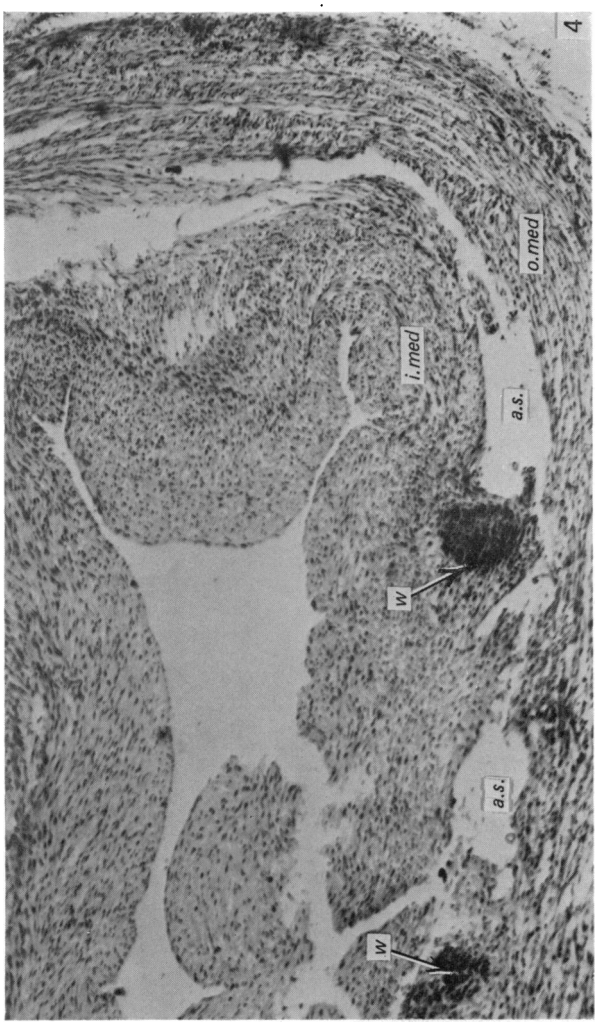
The intima consisted of an endothelial cell lining with subendothelial avascular connective tissue.

Ductal closure

The ducts varied in patency from widely patent to totally occluded. From a study of these it was possible to deduce a scheme of the histological changes involved in closure (Fig. 2).

In two specimens the anticipated one cell thick intima was observed to have an irregular appearance, being many cells thick in places (Fig. 3). Accompanying this, the inner media was less dense than normal, showing an increase of ground substance between the muscle fibres. The ground substance contained a moderate amount of very fine wavy elastic fibres amongst the collagenous fibres.

In 23 specimens the inner media was thrown into mounds of cellular proliferation, while the intima remained as a thin layer. In cases of advanced medial proliferation, cellular elements could be seen penetrating gaps in the fragmented elastic membrane (Fig. 3), and extending into the region between the intima and the internal elastic membrane. In many specimens, the muscle fibres appeared degenerate, and in six of these, groups of degenerating muscle cells could be seen as little whorls in the inner media away from the orifice of the ductus (Fig. 4). These degenerating cells had indistinct cell membranes, and their densely stained nuclei appeared elliptical. Tiny, wavy elastic fibres occurred among these cells. Acellular spaces were often found next to these cellular whorls. The spaces were filled with a hyaline-like mucoid material. In these six specimens the spaces represented a zone of potential delamination of inner from outer media.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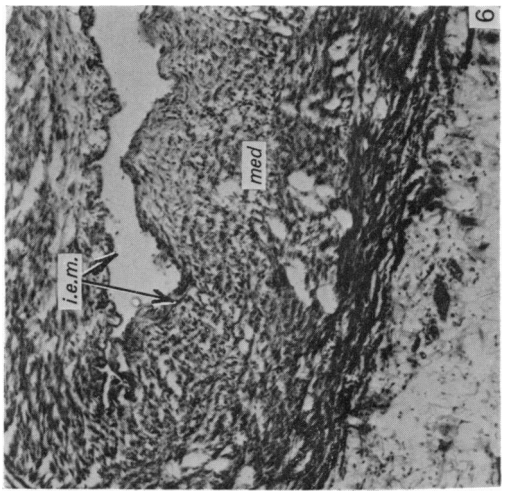
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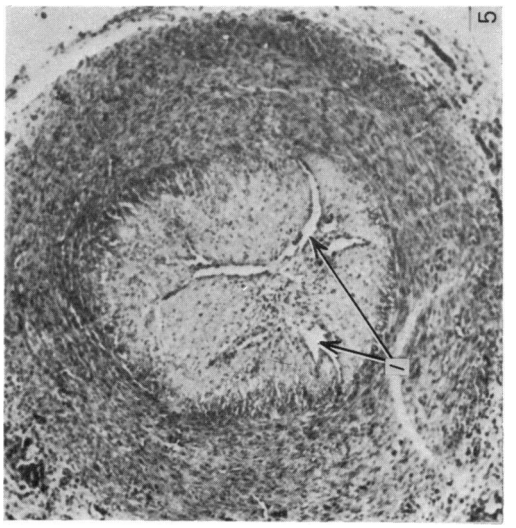
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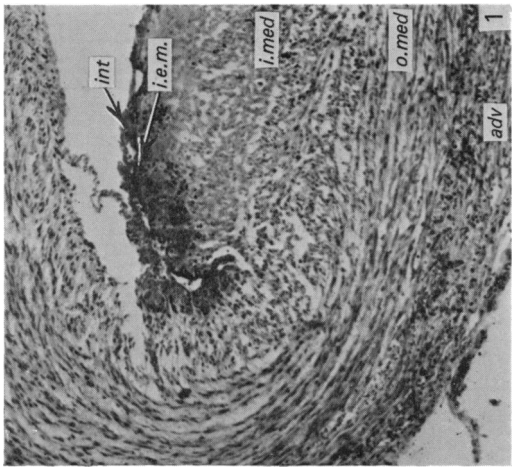
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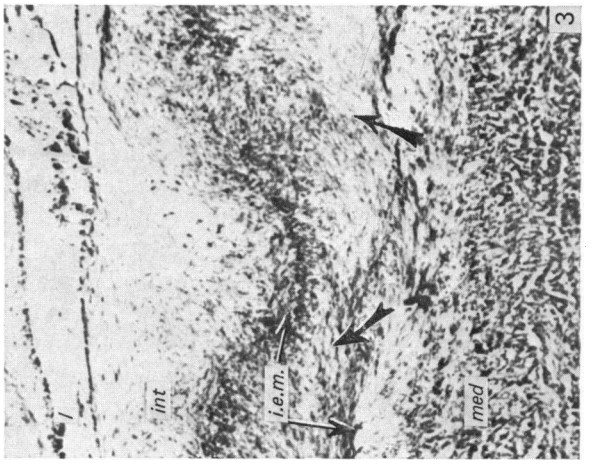
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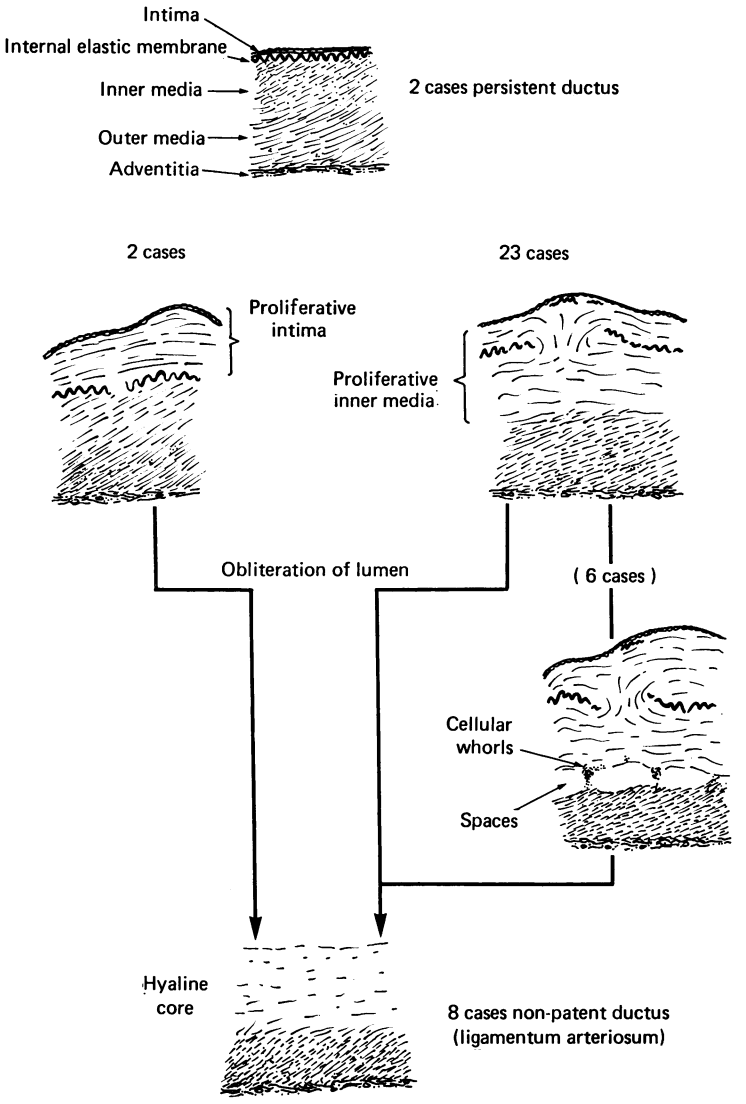

Fig. 2. A scheme showing the processes of anatomical ductal obliteration as deduced in this study.

Fig. 1. Transverse section of a normal ductus. A fragmented internal elastic membrane (i.e.m) separates the intima (*int*) frpm the inner media (*i.med*). The inner media, outer media (*o.med*) and the adventitia (*adv*) are not well defined from each other. Trichrome. × 60.

Fig. 3. Part of a longitudinal section of a nearly obliterated ductus. The lumen (*l*) is very narrow. The intima (*int*) as well as the media (*med*) have proliferated. The internal elastic membrane (*i.e.m*) is disrupted and media tissue occupies the sub-intimal space (arrows). Verhoeff's Van Gieson. × 100.

Fig. 4. Section of a ductus to show the cellular whorls (*w*). The acellular spaces (*a.s*) lie between the inner media (*i.med*) and outer media (*o.med*). Trichrome. × 60.

Fig. 5. Stellate lumen (*l*) in a cross section of an obliterated ductus. Trichrome. × 50.

Fig. 6. The internal elastic membrane (*i.e.m*) is intact and lines the lumen of the persistent ductus. The media (*med*) shows little evidence of proliferation. Trichrome. × 60.

In specimens in which the ductal lumen was narrow, the smooth muscular cells were less conspicuous, while the collagenous ground substance was more evident. The endothelium in these ducts could no longer be identified as a distinct layer. In cross section the lumen appeared stellate or irregular (Fig. 5). It appeared as a slit in longitudinal sections. In closed ducts the intima and inner media had lost their cellular characteristics and become a hyaline mass. Throughout the obliterative process, the adventitia and outer media remained structurally intact.

Persistent ductus

Two cases of persistent ductus were encountered in this study (Cases 10, 22). They were structurally comparable to the other ducts except for a very distinct and virtually intact internal elastic membrane (Fig. 6). The intima was one cell thick and protrusion into the ductal lumen was minimal. The media did not show such marked histological changes as in the normal ducts. Smooth muscle fibres could be discerned easily, and elastic fibres were more abundant in the ground substance. These elastic fibres, however, were not organized into lamellae as in the great arteries.

DISCUSSION

Early speculations concerning ductal closure included direct adhesion of the ductal walls (Rokitansky, 1852), traction resulting from a shift in position of the thoracic organs following the onset of respiration (Chevers, 1854), compression of the ductus (Noback & Rehman, 1941), and development of a flap-like 'valve' at the aortic end (Strassman, 1894; Fay & Travill, 1967). Through histological studies, however, most authors now consider that the ductus goes through an active morphological process characterized by an abundance of connective tissue and metachromatic ground substance (Jager & Wollenman, 1942; Danesino *et al.* 1955; Jones *et al.* 1969; Desligneres & Larroche, 1970; Broccoli & Carinci, 1973; Gittenberger-de Groot, 1977).

From the present investigation it has been possible to deduce the course of anatomical ductal obliteration. Essentially, it is a gradual process and involves an increase in ground substance in the media accompanied by proliferations of the intima or media tissue into mounds, the occurrence of mucoid-filled spaces, and the fragmentation of the internal elastic membrane. In the final stages, the intima and inner media are converted to a hyaline mass, obliterating the lumen. This is in general agreement with the views of such other workers as Bakker (1962) and Gitternberger-de Groot (1977). We will emphasize some salient points of difference, however.

The mounds or protrusions into the vascular lumen, the most outstanding features of a normal obliterating ductus, are generally thought to be the result of internal proliferation (Costa, 1930; Jager & Wollenman, 1942; Everett & Johnson, 1951; Danesino *et al.* 1955; Sciacca & Condorelli, 1960). However, Noback, Anderson & Cooper (1951) and Desligneres & Larroche (1970) pointed out that in some cases they are really thickenings of the media. If the intima is defined as that portion of the wall which lies within the internal elastic membrane, then the present study supports the latter contentions that the ductal lumen is obliterated mainly by proliferation of the inner media and only to a lesser extent by the proliferation of the intima. This is suggested by the great thickness of the media, disruption of the internal elastic membrane, and minimal thickness of the intima. Some fragments

of the elastic membrane appeared to have been carried toward the lumen, and others left behind, while the proliferating media spread into the subendothelial region. It is suggested that the internal elastic membrane may break down under the combined stress of the proliferating inner media and maintained contraction of the outer media. Workers on animal material have made analogous observations which support the contention that the mounds are of medial origin. For instance, Jones *et al.* (1969), with the electron microscope, observed extensions of the smooth muscle cells of the media through the internal elastic membrane in rats.

A dissociation of the inner media, as reported by Meyer & Simon (1960) and Hoffman (1964), was observed in six cases here. This has been thought to be a prenatal preparation for ductal closure. However, as this dissociation was only observed in six cases, all of which were postnatal, we are of the opinion that it is not a major factor in ductal obliteration. The zone of delamination was marked by large accellular spaces and cellular whorls. Jager & Wollenman (1942) are the only other authors to have reported cellular whorls, the significance of which are not clear.

The fact that nearly all the ducts studied, ranging in age from newborn to 2¼ years, showed tendencies towards closure, indicated that the human ductus begins to close during fetal life. This process may in some cases be prolonged to the first few years of neonatal life. It is therefore difficult to define clearly a period within which a ductus must close or else be designated as persistent. Although it is generally agreed that patency after one year should be considered persistent (Gerard, 1900; Scammon & Norris, 1918; Christie, 1930; Edwards, 1953), Cassels' (1973) review of published data indicated that anatomical closure generally occurs within 3 months. Gittenberger-de Groot (1977) discussed the difficulties encountered in distinguishing between prolonged patency and persistence of the ductus in the clinical setting. In agreement with her, our two cases of apparently persistent ductus showed continuity of the elastic membrane, and rather more elastic tissue in the media, than in the other specimens. Owing to this histological difference, it is possible that such persistent ducts may not have the same reaction to drugs such as indomethacin (which induces closure) or prostaglandins (which prevent closure) as other ducts. Apart from the two cases of isolated persistent ductus, we found some 'life-line' ducts (in association with such anomalies as aortic atresia, aortic stenosis or obstruction or coarctation) which nevertheless showed tendencies towards closure. Therefore, ductus persistency may well be a primary anomaly (Gittenberger-de Groot, 1977).

SUMMARY

The process of anatomical ductal obliteration appears to be gradual and to involve proliferation of intima and media (mainly the latter) producing mounds, mucoid-filled spaces and fragmentation of the internal elastic membrane. Dissociation of the inner media may also be involved. The persistent ductus can be recognized histologically, and its clinical significance is discussed.

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