

Iliac arteries in children with a single umbilical artery

Structure, calcifications, and early atherosclerotic lesions

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Meyer, W. W., and Lind, J. (1974). *Archives of Disease in Childhood*, **49**, 671. **Iliac arteries in children with a single umbilical artery: structure, calcifications, and early atherosclerotic lesions.** With a single umbilical artery a unique haemodynamic situation arises during fetal development, resulting in a different calibre and structure of the iliac arteries on the two sides of the body. On the side of the single umbilical artery, the enlarged iliac arteries have the structure of elastic arteries, whereas the smaller and thin-walled iliac arteries, which do not participate in the placental circuit, show the typical structure of muscular arteries. These differences of the arterial structure determine the morphological pattern of early calcifications which are regularly present in the iliac arteries on both sides of the body, but are usually more conspicuous in the large iliac arteries on the side of the single umbilical artery. In 2 children, aged 18 months and 4 years, atherosclerotic lesions were present in the wide common iliac artery on the side of the obliterated single umbilical artery. These lesions represent the earliest atherosclerotic changes to be found in the human. They are probably related to the remodelling of these arteries, beginning after birth as an adaptation to decreased blood flow.

Aplasia of one umbilical artery occurs in 0.75–1.1% of consecutive deliveries and is frequently associated with congenital malformations (Benirschke and Bourne, 1960; Faierman, 1960; Thomas, 1961; Fujikura, 1964; Seki and Strauss, 1964; Fujikura and Froehlich, 1972). Therefore, children born with a single umbilical artery (SUA) in the umbilical cord are subject to special attention by obstetricians and paediatricians. Moreover, this vascular anomaly is of particular angiological interest because of the unique haemodynamic situation arising during fetal development. In fetuses with a single umbilical artery, the whole blood flow to the placenta is transported through the common iliac and internal iliac arteries of one side of the body, whereas the iliac arteries of the other side of the body do not participate in the placental circuit. Consequently, the common and internal iliac arteries on the side of the SUA become subject to a higher haemodynamic load and achieve a considerably larger calibre than those on the other side of the body (Fig. 1).

The purpose of this study is to show that these differences in calibre are regularly associated with different structural patterns of the arterial wall, and that the large iliac arteries which were initially subjected to a higher functional load early become the site of predilection for calcific and atherosclerotic lesions.

Materials and methods

Eight children aged 2½ days to 4 years with single umbilical artery were studied. Congenital malformations were present in 3 cases (Table I). The iliac arteries were removed from the body with the lower part of the abdominal aorta and the abdominal part of the single umbilical artery. In all but one case (Case 7), the iliac arteries were opened longitudinally along their medial retraction folds (see Meyer and Lind, 1972). The specimens were then rinsed with distilled water, and the calcific deposits demonstrated grossly with the modified von Kossa reaction (Meyer and Stelzig, 1969a). As in our earlier study, the gross calcifications were arbitrarily classified into grades I–III. In Case 7, the arteries were removed from the body and examined microscopically after formalin fixation *in situ*. In Cases 2 and 4, a combined gross demonstration of calcific and

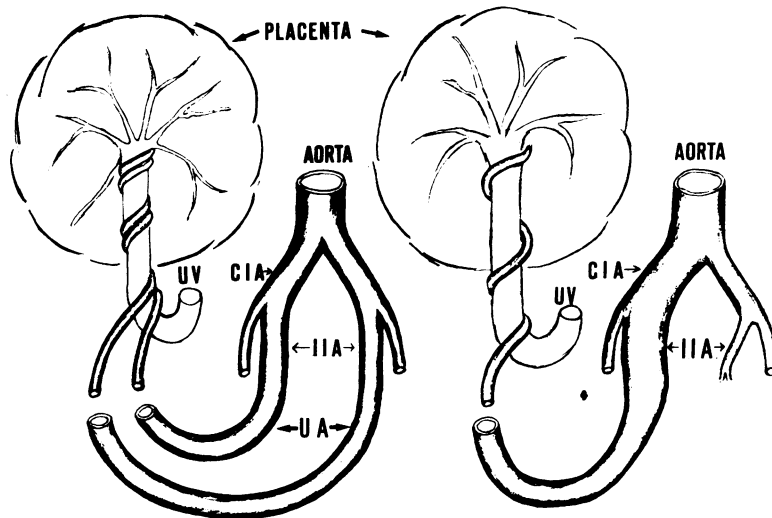


FIG. 1.—Diagram of the iliac arterial tree in normal fetus with 2 umbilical arteries (left); and in fetus with a single umbilical artery (right); showing different calibres of the 2 iliac arteries. UA, umbilical artery; UV, umbilical vein; CIA, common iliac artery; IIA, internal iliac artery.

lipid deposits was used. Frozen cross and longitudinal cryostat sections were prepared for microscopical examination and stained with Gomori's aldehyde fuchsin, Weigert's resorcin-fuchsin, orcein, Fettrot VII B, and other conventional methods.

Results

Anatomical findings. In 5 cases the left umbilical artery was absent and in 3 cases the right. The common and internal iliac arteries on the side of the SUA were wide and thick-walled as compared to

the iliac arteries on the other side of the body (Fig. 2, 3, 4, and Table II). In comparison to the normal values (Meyer and Lind, 1972), the iliac arteries on the side of the SUA appeared larger than the normal arteries of corresponding age. In contrast, the iliac arteries which did not participate in the placental circuit were significantly smaller than normal arteries. The differences in size of the iliac arteries on both sides of the body tended to diminish with advancing age.

In one case only (Case 1, Table I), an anomalous

TABLE
Findings in children with a

Case no.	Age	Sex	Body length (cm)	Body weight (kg)	SUA
1	13 mth	F	73	15	L
2	18 mth	M	79	9.7	R
3	5 dy	F	44	2.150	R
4	4 yr	F	116	30	R
5	4 dy	M	34	0.62	R
6	2½ dy	M	50	3.200	L
7	—	F	—	—	R
8	1 mth	M	57	3.45	L

*Grades I-III, arbitrary classification.

TABLE II

Circumference (mm) of abdominal aorta and iliac arteries in children with a single umbilical artery (SUA)

Case no.	SUA	Abdominal aorta	Common iliac		Internal iliac		External iliac	
			R	L	R	L	R	L
2	R	12	9	6	5.5	4	5	5
3	R	—	7	4	7	—	—	—
4	R	17	13	10	9	6.5	9	9
6	L	14	5	8	3.5	9	4	4
8	L	12	4	9	3.5	6	4	4

No measurements were made in Cases 1, 5, and 7.

branching of the iliac arteries on the side of the SUA was present. In this case, both the external and the internal iliac artery originated from the bifurcation of the abdominal aorta.

Microscopical structural patterns. In the premature twin (Case 5) the common iliac arteries of both sides of the body showed an identical structural pattern (Fig. 5). Their media consisted of concentrically arranged elastic membranes with narrow interlamellar spaces between. Thus, both arteries represented elastic arteries. However, the wall of the small common iliac artery which did not participate in the placental circuit was approximately only one-quarter the thickness of the common iliac artery on the side of the SUA. At term (Case 6), the right and the left common iliac arteries showed not only a pronounced difference in the wall thickness, but also a quite different structural pattern of their media (Fig. 6). The left common and internal iliac arteries on the side of the SUA had the structure of elastic arteries, with tightly packed,

interconnecting elastic membranes in their media. By contrast, the smaller right common and internal arteries had the typical structural pattern of a muscular artery, their media consisting predominantly of smooth muscle with a poverty of elastic elements (Fig. 6B).

Similar unequivocal differences in the wall thickness and medial structure were also found in Cases 1, 2, 4, and 8. However, with growth, the interlamellar spaces of the elastic arteries on the side of the SUA became wider and included more muscle cells compared with the corresponding arteries of the newborn subjects. The smaller iliac arteries, which did not participate in the placental circuit, retained the structural pattern of muscular arteries (Fig. 7).

Early calcifications. Gross calcifications of the iliac arteries were shown by the von Kossa reaction in 6 of 8 cases (see Table I). In all but one (Case 8, Fig. 4), the calcifications were more conspicuous in the larger iliac arteries on the side of

I
single umbilical artery (SUA)

Grade of gross calcifications of iliac arteries*				Atherosclerotic lesions	Main illness
On the side of SUA		On the opposite side			
Common iliac	Internal iliac	Common iliac	Internal iliac		
II		I	0	—	Extensive burns
(common iliac trunk)					
III	I	II	0	+	Congenital hydrocephalus
I	0	0	0	—	Prematurity; perinatal asphyxia
I	II	0	0	+	Spongioblastoma of medulla oblongata
0	0	0	0	—	Prematurity; twin
II	I	I	0	—	Cerebral birth injury
(medial calcification)					
0	0	0	0	—	Thoracopagus; malformations of both hearts
II	III	III	I	—	Multiple congenital malformations: Fallot's tetralogy; oesophageal atresia

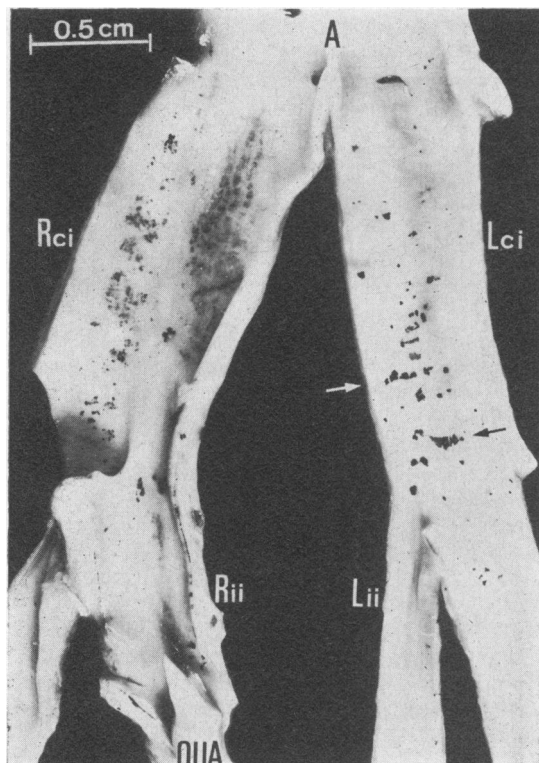


FIG. 2.—Case 2. Iliac arteries of an 18-month-old girl. The luminal layer of the larger right common iliac artery (Rci) on the side of the obliterated single umbilical artery (OUA) is densely interspersed with irregularly distributed fine calcific incrustations (black). These are partly covered with a thickened intima and hence poorly outlined. In the smaller left common iliac artery (Lci), the well-outlined calcific incrustations tend to form circular bands (arrows). Note also the different calibre of the right (Rii) and the left internal iliac artery (Lii). A, aortic bifurcation. See colour plate A.

the SUA. In these arteries, the calcific deposits were irregularly distributed over the arterial luminal surface, whereas in the narrower iliac arteries on the other side of the body the pattern of calcification was more regular.

On the side of the SUA, the large common iliac arteries showed numerous fine roundish incrustations, often densely interspersed over the arterial luminal surface, and irregularly distributed over the dorsolateral and/or anterolateral arterial wall (Cases 1, 2, 4, 8; Fig. 2, 3, 4). Microscopically, they represented calcifications of the internal elastic membrane (colour plate B). However, in one newborn (Case 6), the large common iliac artery on

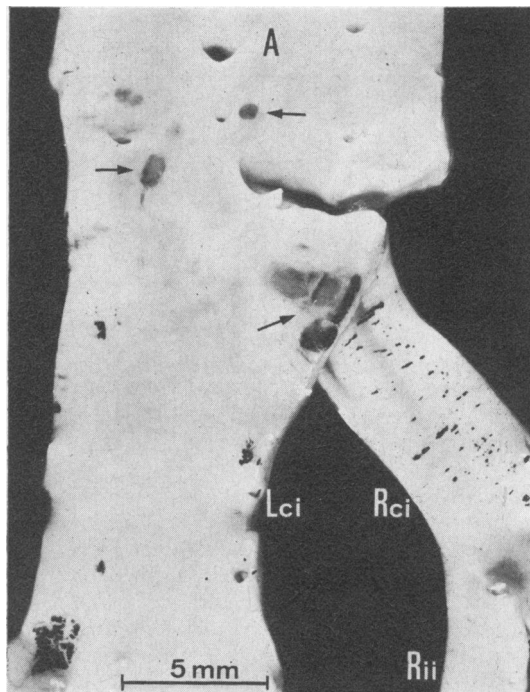


FIG. 3.—Case 6. Lower abdominal aorta (A) and the iliac arteries of a newborn infant with a single left umbilical artery (dorsal view). After the von Kossa reaction, large plaque-like incrustations (black) are seen at the origin of the enlarged left common iliac artery (Lci) on the side of the single umbilical artery and in the lower abdominal aorta (arrows). The lesions are partly covered with thickened intima. Scattered, well-delineated membrane calcifications (black) are present in other parts of the artery. In the right common iliac artery (Rci) the calcifications appear as fine linear circular incrustations. No calcium deposits are present in the right internal iliac artery (Rii).

the side of the SUA showed not only superficial membrane calcifications, but also conspicuous plaque-like medial calcifications which were irregularly distributed over the wide origin of the artery and were also present in the adjacent lower abdominal aorta (Fig. 3 and 8).

In the smaller common iliac arteries on the other side of the body, the calcifications seemed to extend in a circular pattern, and appeared as fine transverse streaks (Fig. 2 and 3). In another case (Case 8), pairs of circular, band-like calcific incrustations were seen on both borders of the well-delineated transverse calcific-free stripes (Fig. 4). Microscopically, these stripes corresponded to the wide transverse gaps in the internal elastic membrane, whereas the

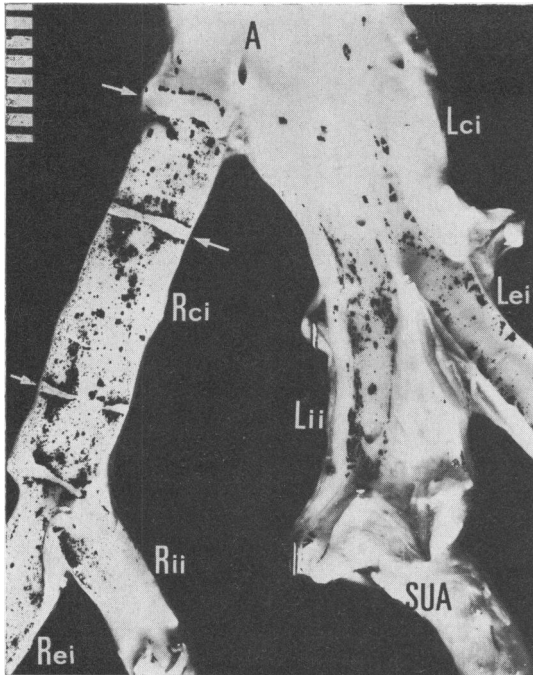


FIG. 4.—Case 8. Iliac arteries of 1-month-old child with a single (left) umbilical artery. Note the large calibre of the common iliac artery (Lci) and that of the internal iliac artery (Lii) on the side of the closed umbilical artery. Conspicuous calcifications (black) of both iliac arteries. Note different calcification patterns of the iliac arteries on the side of the single umbilical artery. (von Kossa. mm scale top left.)

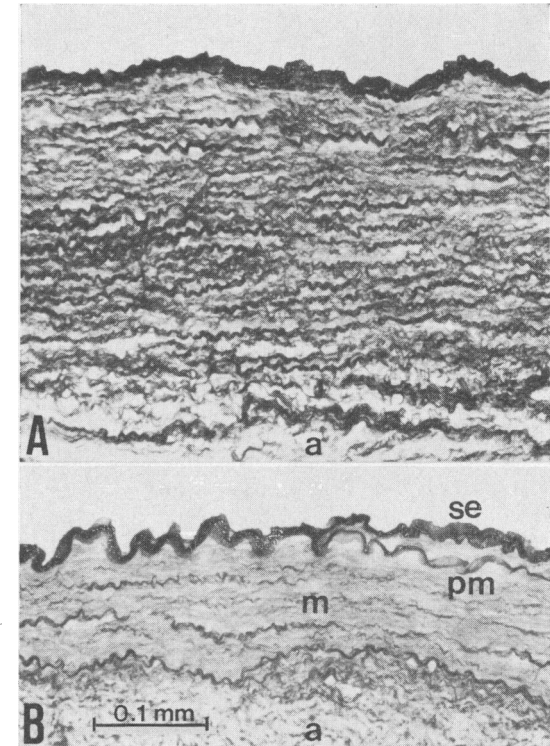
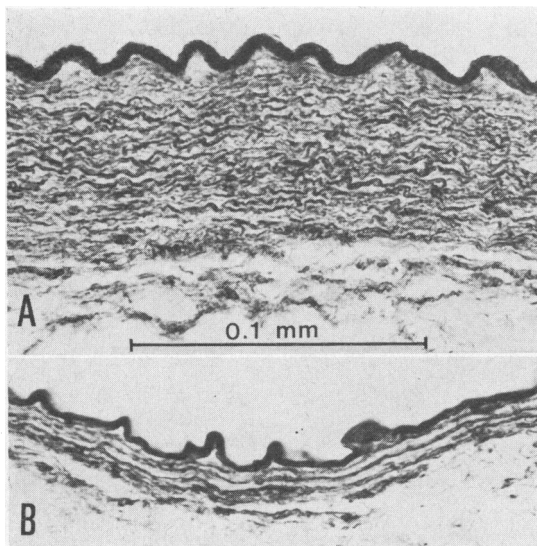
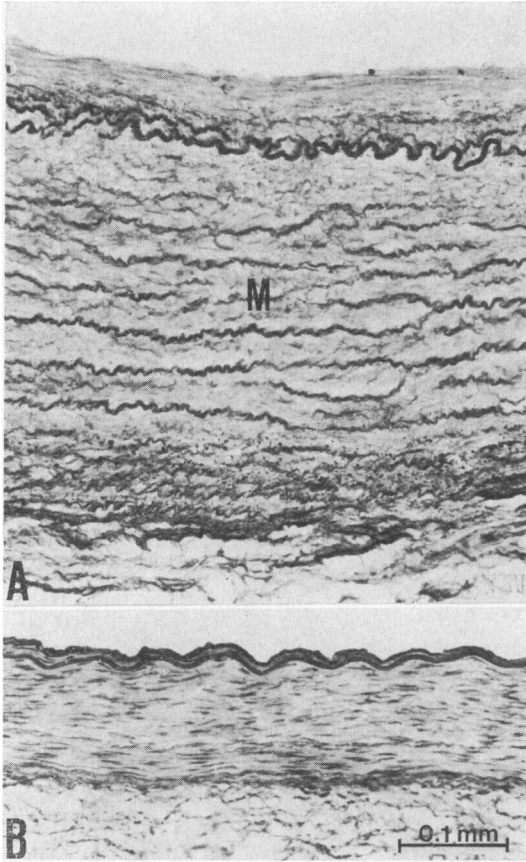


FIG. 6.—Case 6. Cross-sections of common iliac arteries of a newborn infant delivered at term. On the side of the single umbilical artery, the common iliac artery (A) is an elastic artery with well-developed elastic sheets in its media. In contrast, the thin-walled iliac artery, which did not participate in the placental circuit (B), displays the pattern of a muscular artery with a media (m) poor in elastic networks; pm, primary internal elastic membrane; se, secondary subendothelial elastic networks; a, adventitia. Cryostat frozen section. (Weigert's resorcin-fuchsin.)

band-like incrustations on both sides of these gaps represented the edges of calcified membrane. The transverse black linear or streak-like incrustations, which were found in the narrower common iliac arteries of other children born with an SUA, also represented calcific deposits in the edges of the interrupted internal elastic membrane.

Thus, the more regular distribution of calcific

FIG. 5.—Case 5. Cross-sections of (A) right and (B) left common iliac arteries of a premature twin. Both vessels show the structural pattern of elastic arteries. On the side of the single umbilical artery the common iliac artery (A) is approximately four times thicker than the opposite artery (B). Cryostat frozen section. (Weigert's resorcin-fuchsin.)



deposits in the narrower iliac arteries of children with SUA depended on the shape and site of the gaps in the internal elastic membrane. The system of these membrane gaps represents a characteristic structural feature of most human muscular arteries, and it determines the morphological aspect of the early arterial calcifications (Meyer and Stelzig, 1969b). Hence, the calcification patterns shown in the narrower iliac arteries, which did not participate in the placental circuit and which represented muscular arteries, accorded with their structural pattern.

Atherosclerotic lesions. Gross atherosclerotic lesions were present in the larger common iliac arteries on the side of the obliterated SUA in 2 children aged 18 months and 4 years. In the right common iliac artery of the 18-month-old child (Case 2), yellowish spot-like inclusions were seen in the midst of dense calcifications (shown by the von Kossa reaction). After staining of the lipid, two longitudinal, intensely red stripes appeared in the lateral arterial wall (colour plate A), and a triangular

FIG. 7.—Case 2. Cross-sections of (A) enlarged right common iliac artery on the side of the obliterated umbilical artery, and (B) of the smaller left common iliac artery on the opposite side of an 18-month-old child (see Fig. 2). Whereas the right common iliac artery (A) displays the microscopical structure of an elastic artery with numerous lamellar units in its media (M), the left common iliac artery (B) shows a structural pattern of a muscular artery. (See also colour plates A and B.) (Orcein stain. $\times 146$.)

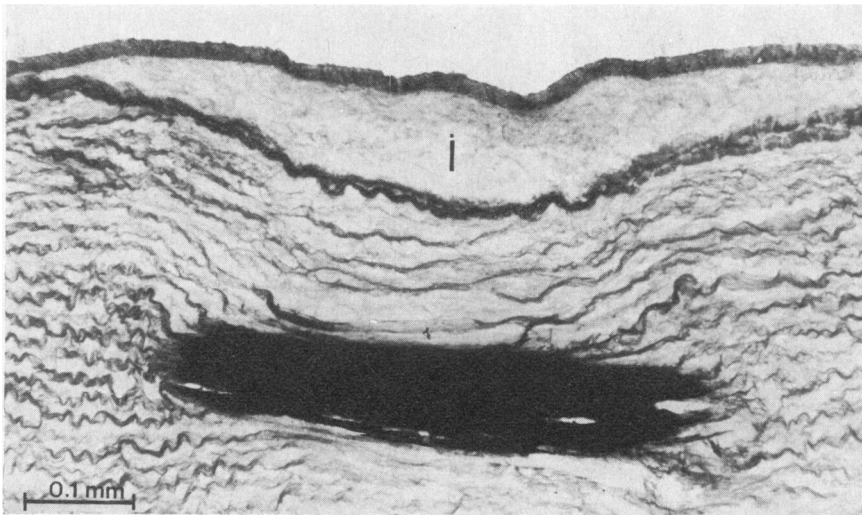


FIG. 8.—Case 6. Medial calcification of the abdominal aorta above the origin of the enlarged common iliac artery on the side of a single umbilical artery. (See Fig. 3.) Circumscribed intimal thickening (I) above the calcified area. Cryostat frozen section. (von Kossa reaction and Gomori's stain for elastic tissue.)

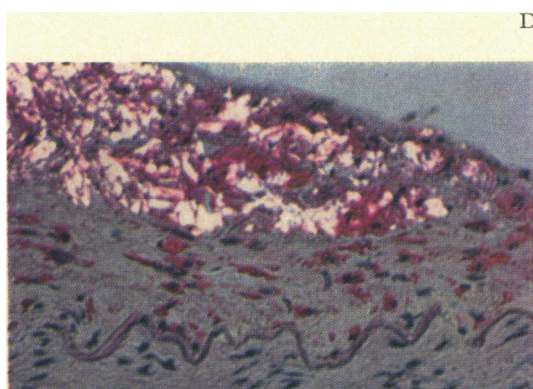
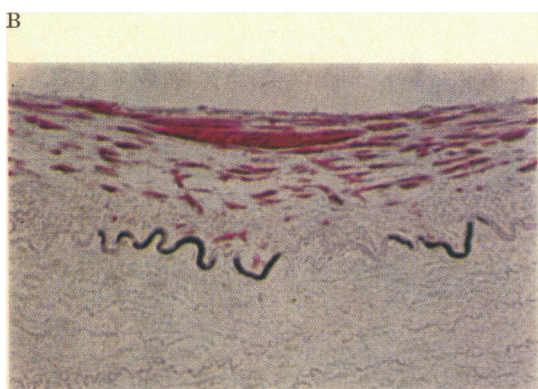


PLATE A.—Case 2, 18 months old. Calcific (black and brown) and lipid (red) deposits in the right common iliac artery on the side of the obliterated single umbilical artery (see also Fig. 2). Two longitudinal intensely red-stained lipid deposits are seen in the middle part of the artery. A poorly outlined red-stained area extends from the upper part of the artery to the bifurcation of the aorta. mm scale top left. See also colour plate B.

PLATE B.—Case 2, 18 months old. Cross-section of the right common iliac artery seen in colour plate A. In the area of the lipid deposits the intima is much thickened and densely interspersed with fusiform and star-like cells containing lipid inclusions (red). The underlying internal elastic membrane is partly calcified (black). Cryostat frozen section. (von Kossa reaction and Fettrot VII B stain. $\times 400$.)

PLATE C.—Case 4, aged 4 years. A longitudinal red-stained early atherosclerotic lesion in the enlarged right common iliac artery on the side of the obliterated single umbilical artery. In the narrower left common iliac artery many fine circular folds ('spindles') are discernible. Fine calcific incrustations (brown) are present in the right internal iliac artery. mm scale top right. See also colour plate D.

PLATE D.—Case 4, aged 4 years. Numerous anisotropic crystals and lipid droplets in the microscopical cross-section of the intimal plaque in colour plate C. Cryostat frozen section. (Fettrot VII B stain. $\times 400$.)

area diffusely red-stained also became visible in the proximal part of the artery. It extended proximally to the bifurcation of the aorta and surrounded the orifice of the caudal artery. A poorly demarcated reddish zone was seen below the intensely stained longitudinal fatty streaks.

Microscopically, the intima of the common iliac artery was moderately thickened and appeared in cross-section of the artery as a sickle-shaped layer superimposed on the media. In the central sector, i.e. where the intima was thickest, numerous spindle-shaped and star-like fat-containing cells were seen amidst the fine collagenous intimal networks. Occasionally, these fat-containing cells formed larger longitudinal aggregates in the thickened intima (colour plate B). Numerous fine anisotropic inclusions were seen in these areas. The primary internal elastic membrane below the lipid infiltrated intima and in the adjacent sectors showed conspicuous calcific incrustations (colour plate B).

Even more striking, early atherosclerotic lesions were found in the large right common iliac artery on the side of the obliterated SUA in a 4-year-old girl (Case 4). After lipid staining, a 2 cm long, slightly raised intense red stripe appeared in the dorsal wall of the artery. No lipid deposits were seen in the smaller left common iliac artery or in the abdominal aorta (colour plate C).

Microscopically, on cross-section of the involved area (colour plate D), the intima was thickened and rich in collagenous networks. A protruding, circumscribed collection of large, tightly packed fat-containing macrophages was present in the luminal layer. Numerous anisotropic crystals, probably cholesterol, were present in these cells and in the debris between them. The underlying intima showed spindle-shaped fat-containing cells embedded in the collagenous networks. Calcifications of the internal elastic membrane were occasionally present beneath the involved intima.

Discussion

During fetal development, the common and internal iliac arteries on the side of the SUA represent the only connexion between the fetal abdominal aorta and the placental circuit. Therefore they are exposed to a higher blood flow than are the iliac arteries on the other side of the body, or the iliac arteries in fetuses with two umbilical arteries. Hence, the large calibre of the iliac arteries on the side of the SUA obviously represents a structural adaptation to a higher haemodynamic load. With the adaptive increase in calibre, the total wall tension of the arterial tube also increases even if the blood

pressure remains unchanged (Law of Laplace). The higher wall tension favours the development of the elastic elements in the arterial wall and determines the structural pattern of the common and internal iliac arteries which consequently develop as elastic arteries on the side of the SUA. In contrast, the total wall tension of the narrow iliac arteries which do not participate in the placental circuit is lower and may correspond to the tension of the peripheral muscular arteries of comparable diameter. Therefore, the muscular pattern of the narrow iliac arteries appears adequate for their lower functional load. However, the marked structural differences of the iliac arteries in children with SUA may also result from disturbed development of the iliac arterial tree and so represent an associated developmental anomaly.

The early calcifications tend to be more conspicuous in the large iliac arteries on the side of the SUA. They are probably favoured by the early wear and tear changes of the elastic elements, which may result from the higher wall tension in a rapidly growing and widening arterial tube.

The atherosclerotic changes found in the large iliac arteries on the side of the obliterated SUA in 2 cases are of special interest because they belong to the earliest atherosclerotic lesions of the human arterial system. In this connexion, fatty streaks, the first signs of beginning atherosclerosis, do not usually appear in the iliac arteries before the end of the first decade of life (Bernauer, 1968).

Since no 'fatty streaks' were present in other arterial provinces, general metabolic factors are probably not involved. The selective development of early atherosclerotic lesions in the iliac arteries on the side of the SUA appears rather to be the result of some local structural and haemodynamic factors. However, as no lipid deposits were present in the large iliac arteries of the newborn children with SUA, the lesions could not be the immediate consequence of the higher functional load to which these arteries are subjected during fetal development, and which probably promote the early calcifications. The early atherosclerotic lesions obviously appear later and probably begin with the remodelling of the enlarged iliac arteries, starting after birth and constituting a structural adaptation to the much diminished blood flow after the cessation of the umbilical circulation. This adaptation includes the proliferation of the intima which contributes to the narrowing of the lumen. Numerous experiments have shown how various local injuries of the arterial wall, that are associated with or are followed by intimal proliferation, promote the development of cholesterol-induced

atherosclerosis (Taylor, 1955; Hass, Truehart, and Hemmens, 1961; Cox *et al.*, 1963). Similarly, the proliferating intima of the large iliac arteries may also achieve an increased 'lipidosis potential' (Hass, 1967), and in this way become the site of predilection for atherosclerotic lesions. Additionally, the adaptive contraction and thickening of the media, which occurs after the umbilical circulation ceases, may interfere with the normal nutrition and metabolism of the arterial wall and so also favour deposition of lipids in the thickened intima.

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REFERENCES

- Benirschke, K., and Bourne, G. L. (1960). The incidence and prognostic implication of congenital absence of one umbilical artery. *American Journal of Obstetrics and Gynecology*, **79**, 251.
- Bernauer, K. V. (1968). Die Entwicklung der Lipoidablagerungen ('Lipoidflecke') in den Arterien des Beckens und der unteren Extremität. *Inaugural—Dissertation (Thèse)*, Mainz.
- Cox, G. E., Trueheart, R. E., Kaplan, J., and Taylor, C. B. (1963). Atherosclerosis in rhesus monkeys. IV. Repair of arterial injury—an important secondary atherogenic factor. *Archives of Pathology*, **76**, 166.
- Faierman, E. (1960). The significance of one umbilical artery. *Archives of Disease in Childhood*, **35**, 285.
- Fujikura, T. (1964). Single umbilical artery and congenital malformations. *American Journal of Obstetrics and Gynecology*, **88**, 829.
- Fujikura, T., and Froehlich, L. (1972). A follow up of children with single umbilical artery. *American Journal of Pathology*, **66**, 19a.
- Hass, G. M. (1967). The pathogenesis of human and experimental athero-arteriosclerosis. In *Cowdry's Arteriosclerosis. A Survey of the Problem*, 2nd ed., p. 689. Ed. by H. T. Blumenthal. Thomas, Springfield, Illinois.
- Hass, G. M., Trueheart, R. E., and Hemmens, A. (1961). Experimental athero-arteriosclerosis due to calcific medial degeneration and hypercholesterolemia. *American Journal of Pathology*, **38**, 289.
- Meyer, W. W., and Lind, J. (1972). Calcifications of iliac arteries in newborns and infants. *Archives of Disease in Childhood*, **47**, 364.
- Meyer, W. W., and Stelzig, H. H. (1969a). A simple method for gross demonstration of calcific deposits in the arteries. *Angiology*, **20**, 423.
- Meyer, W. W., and Stelzig, H. H. (1969b). Calcification patterns of the internal elastic membrane. *Calcified Tissue Research*, **3**, 266.
- Seki, M., and Strauss, L. (1964). Absence of one umbilical artery. *Archives of Pathology*, **78**, 446.
- Taylor, C. B. (1955). The reaction of arteries to injury by physical agents with a discussion of arterial repair and its relationship to atherosclerosis. In *Symposium on Atherosclerosis*, p. 74. National Research Council Publication No. 338. National Academy of Sciences, Washington, D.C.
- Thomas, J. (1961). Untersuchungsergebnisse über die Aplasie einer Nabelarterie unter besonderer Berücksichtigung der Zwillingschwangerschaft. *Geburtshilfe und Frauenheilkunde*, **21**, 984.

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