tissue cultures of the developing mammalian cerebellum[12–14]. However, treatment of young animals with thyroid hormones increases the sizes of the neurons and the density of axons in the central nervous system[15–17].

This difference between the effects of thyroid hormones in vivo and in vitro may be due to the fact that many of the afferent and efferent connections of the cultured neurons are necessarily severed by the process of explantation. In this connection it is of interest to note that thyroxine accelerates the degeneration of motor neurons in the spinal cord of the hypophysectomized tadpole, following amputation of the limbs[18]. It is possible that in normal ontogeny the thyroid hormones accelerate the regression of those neurons which differentiate but do not form functional connections.

While triiodothyronine causes degenerative changes in the axons of the cultured cerebellum, thyroxine stimulates the regeneration of axons in the crushed spinal cord of the rat[6]. It is unlikely that this difference represents a differential mode of action of the 2 hormones since these are in all other respects similar, except that T3 is about 10 times as potent as thyroxine[19]. The conflicting observations may, however, be reconciled by the hypothesis that the thyroid hormones accelerate the degeneration of cells whose peripheral connections have been removed. In the cultured fragments many of the afferent and efferent fibres to and from the neurons are severed, while in the crushed spinal cord only the axons are divided, the perikarya, dendrites and afferent synapses of the injured neurons being for the most part remote from the site of axonotmesis. According to the theory, therefore, one would expect treatment with thyroid hormones to produce predominantly regressive changes in culture and predominantly stimulatory effects in the animal with a single localized central nervous lesion.

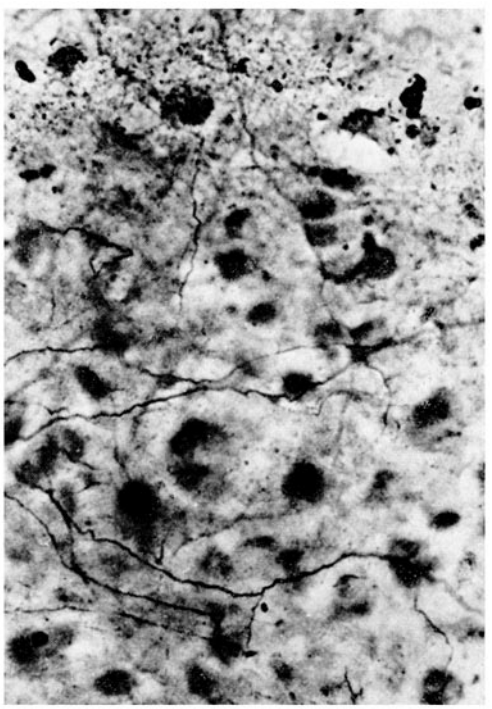

Fig. 4. Culture with T3, 100 ng per ml, showing axons, some of them degenerate, and much argyrophilic debris. Urea-silver nitrate method. ×730.

Résumé. La triiodothyronine produit in vitro des changements régressifs dans les cellules et dans les axones du cervelet du rat nouveau-né. Il est suggéré que les hormones thyroïdes provoquent une dégénérescence accélérée des neurones dont les connexions afférentes et efférentes ont été coupées, tandis qu'elles stimulent la croissance et la différenciation des neurones aux connexions périphériques intactes[20].

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Fibrinolytic Activity in Wall of Human Ductus Arteriosus

It is generally accepted that closure of the ductus arteriosus after birth is brought about by active contraction of the vessel wall followed by intimal proliferation[1–4]. This large shunt, which normally allows $^2/_3$ of the blood ejected from the right heart ventricle to by-pass the high-resistance pulmonary vascular bed[5], is essential for the large foetal cardiac output[6]. Physiological mechanisms for maintaining patency of the ductus in utero have received little attention.

An adequate flow of blood through the ductus is necessary not only for the foetal systemic circulation, but also for nutrition of the ductal wall. The adventitia

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and the outer part of the media of the ductus contain numerous vasa vasorum, but the vessels do not extend to the ductal lumen[7,8]. The intima and the inner part of the media are thus dependent on diffusion of oxygen from the lumen or the outer layers of the ductus. Hence, even temporary contraction of the ductus (claimed to occur in utero[9–12] in this vessel whose receptor and adrenergic innervation apparatus is developed early in the human ontogenesis[13,14]) with cessation of the flow through its lumen would predispose to anoxia in the intima. This, in turn, would cause a release of thromboplastic substances from the endothelium and thereby invite deposition of fibrin with further reduction of oxygen transfer to the inner part of the ductal wall.

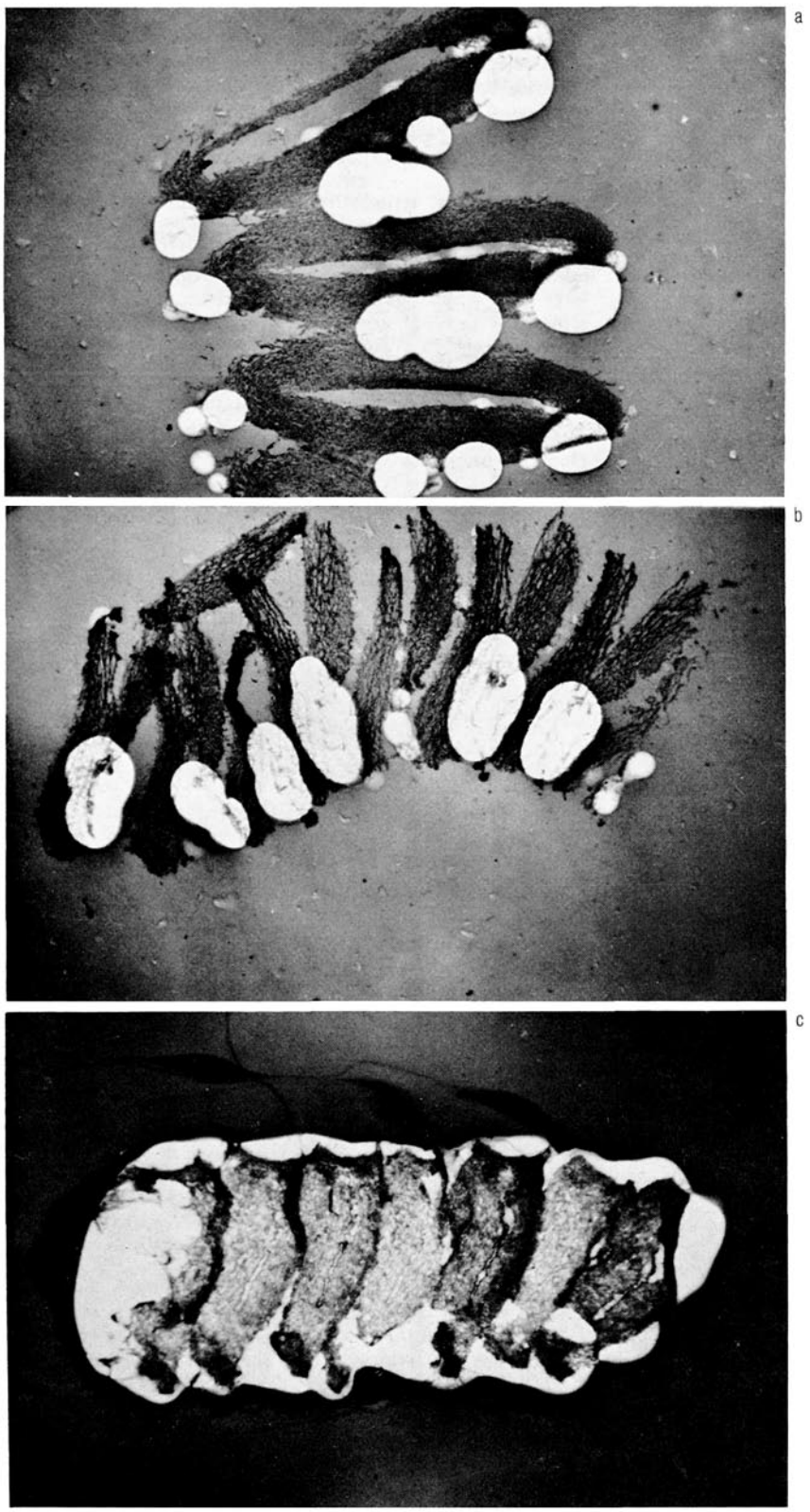

Fig. 2. Cross sections of vessels with same incubation time (45 min) from a foetus of 30 cm crown-heel length. Moderate fibrinolytic activity with circumscript areas of lysis in aorta (upper picture) and pulmonary artery (middle picture). Intense fibrinolytic activity in ductus arteriosus (bottom picture) where all fibrin in contact with sections has been lysed. ×4.1.

Using an extraction procedure, ASTRUP and ALBRECHTSEN[15] have demonstrated plasminogen activator in vessel walls. This finding has been corroborated by TODD[16], who used a 'fibrinolysis autograph technique'. FEARNLEY[17] assumed that activators are continuously liberated from the vessel walls and that they maintain the spontaneous fibrinolytic activity in the blood. It is widely believed that fibrinolytic activity is necessary for preventing deposition of fibrin in the blood vessels and for dissolving any deposits formed[18].

It was therefore considered of interest to assess the fibrinolytic activity in the wall of the human ductus arteriosus. The material consisted of 17 apparently normal 16–23-week-old foetuses (crown-heel length 14.5 to 30 cm) obtained at legal abortions performed by hysterotomy. In 14 cases the ductus arteriosus with adjacent parts of the aortic arch and the pulmonary artery was excised (Figure 1); in 3 the ductus and only one of the adjacent vessels. The vessels were dissected within 20 min after the evacuation of the uterus and immediately frozen in expanding CO_2 or liquid nitrogen.

Values for fibrinolytic activity in human foetal vessel walls, in arbitrary units

Foetal crown-heel length (cm)	Fibrinolytic activity		
	Ductus arteriosus	Adjacent aorta	Adjacent pulmonary artery
14.5	8.5	7.0	3.0
15	8.5	–	7.5
17	10.0	5.5	6.0
17.5	8.5	6.5	8.0
18	6.0	5.5	6.0
18	7.0	4.0	9.0
18.5	9.5	6.0	7.0
19.5	8.0	6.0	–
20	8.5	4.0	7.5
20	11.0	5.5	7.5
21	9.5	–	8.0
22	10.0	3.0	5.0
22.5	10.0	7.0	6.5
24	9.5	7.5	8.0
25	8.5	7.5	3.5
27	8.5	3.5	3.0
30	8.0	4.5	5.0
Mean ± S.E.	8.8 ± 0.3 $n = 17$	5.5 ± 0.4 $n = 15$	6.3 ± 0.5 $n = 16$

Test of difference according to the Wilcoxon rank test for pair differences:

ductus	> aorta	$T_- = 0$	$p < 0.01$
ductus	> pulmonary artery	$T_- = 6$	$p < 0.01$
pulmonary artery	> aorta	$T_- = 32$	$p > 0.1$

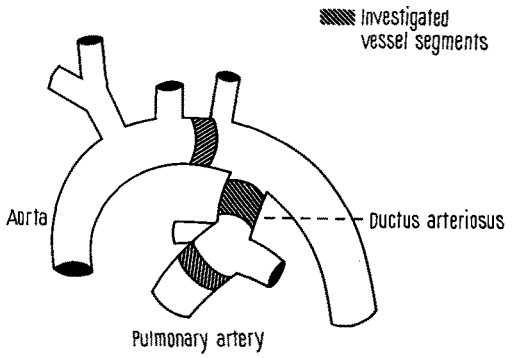

Fig. 1. Topographical relation of the 3 vessel segments investigated.

The fibrinolytic activity was demonstrated with a histochemical method[16] adapted to provide a semiquantitative measurement of the activity[18]. Statistical comparisons between the groups were performed with Wilcoxon's test for pair differences.

The fibrinolytic activator activity in the wall of the ductus arteriosus was high and produced large coalescent lytic areas in the covering fibrin layer in most of the sections. It was significantly higher in the ductal wall than in adjacent parts of the aorta and the pulmonary artery (Table). The zones of lysis were localized to the vasa vasorum in the adventitia and to the intimal endothelium (Figures 2a, b and c). The fibrinolytic activity of the ductus did not vary with the size of the foetus within the range studied.

As known[18], the fibrinolytic activity demonstrated histochemically reflects the quota of fibrinolytic agents readily available for interaction and thereby liable to have a physiological function. In the light of the present consensus of opinion of the function of vascular fibrinolytic agents[17,18] it seems reasonable to assume that the high fibrinolytic activity found in the ductus arteriosus plays a significant role in the prevention of fibrin deposits in the vascular lumen and thereby contributes to the maintenance of the patency of the shunt in utero.

The finding also suggests an ontogenetic differentiation between arteries originating from the embryonic aortic arches. It was found earlier that the contractile response of the ductus to oxygen is peculiar to this vessel[19]. The present investigation provides further evidence of a functional difference between the ductus arteriosus and the adjacent foetal arteries[20].

Zusammenfassung. Die fibrinolytische Aktivität von 17 Ductus Botalli humaner Foeten wurde mit angrenzenden Segmenten der Arteria pulmonalis and der Aorta mit Hilfe der histochemischen Methode nach TODD/PANDOLFI verglichen. Es zeigte sich, dass im Ductus Botalli die fibrinolytische Aktivität im Vergleich zu den beiden anderen Gefässen (sämtliche aus den Aortenbogen entwickelt) höher lag.

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