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[Fifth arch artery – a case of mistaken identity?](#)

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Is it really the artery of the fifth pharyngeal arch that is the “great pretender”?

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In the review published in this issue of the journal,¹ Lloyd and colleagues interpret several rare cardiac malformations on the basis of persistence of the artery of the fifth pharyngeal arch. Following the precedent of Gerlis and his colleagues,² they continue to accord the artery the role of the “great pretender”. One of us was a co-author of the initial work published by Gerlis and his associates that introduced this notion. At that time, however, we did not know - as much about the fate, during development, of the arteries running through the pharyngeal arches. And, as Lloyd and colleagues describe at length,¹ we have collectively now cast significant doubt on the role of the putative fifth arch arteries as the basis of the lesions they now review.^{3,4} In this regard, we also questioned the interpretation of a vessel as a fifth arch artery in a case recently described by Naimo and Konstantinov.⁵ In our letter, however, we mistakenly asserted that the Melbourne authors had “claimed” that the fifth arch artery was involved in their case. As they pointed out in their response, to “claim” is to assert the veracity of any statement. It is the case that, when assessing the role of the fifth arch artery, the best we can do is to speculate.⁶ In their response, however, Naimo and Konstantinov did comment that “this exceptionally rare anomaly does not appear to be of practical medical importance”. This is in contrast to the message from Lloyd and colleagues, namely that “for the clinician, this group of conditions may explain various unusual anatomical features which may be important to recognise when caring for children with congenital heart disease”. The anatomical features emphasized by the group working in London are certainly unusual and of interest. It remains to be established, however, whether they are best interpreted on the basis of persistence of the enigmatic artery of the fifth pharyngeal arch, or whether there are more likely explanations for their morphogenesis.

Much depends, therefore, on our understanding of the events occurring during the development and maturation of the intrapericardial and extrapericardial arterial trunks. In particular, the changes that take place during the formation of the brachiocephalic and pulmonary arteries. According to the current review, “It is a conventionally accepted model that mammals develop six paired pharyngeal arches, which do not co-exist, but variously involute to form the aortic arch and head and neck vessels. The left fourth arch is said to form definitive (left sided) aortic arch, with the developing pulmonary arteries taking their origin from the mid-ventral portions of the sixth arches.” They cite no references to support this allegedly conventional wisdom. In fact, their statement falls short in several regards. In the first instance, our own studies of large numbers of developing mouse embryos have shown that remodeling of the horns of the aortic sac is responsible for producing the brachiocephalic artery and the initial part of the extrapericardial aortic arch (Figure 1).

Figure 1. The images, taken from episcopic datasets prepared from mice sacrificed at embryonic day 10.5 (left hand and central panels) and 11.5 (right hand panel) show how the horns of the aortic sac become remodeled to supply the vessels initially derived from the third and fourth arch arteries. The right hand and left hand panel are shown in the frontal projection, while the central panel shows a view of a sagittal section as seen from the left side. Note that there is no pharyngeal mesenchyme producing an additional arch between the segments containing the fourth and sixth arch arteries.

Our studies then demonstrate that rapid and extensive morphological changes that take place during formation of the subclavian arteries from the seventh cervical intersegmental arteries (Figure 2).

Figure 2. The images show the remodeling of the extrapericardial systemic arteries taking place during embryonic days 12.5 and 13.5. Both are shown in frontal projection. It is the horns of the aortic sac that become the brachiocephalic artery and the proximal component of the transverse aortic arch.

Significant remodeling, therefore, is ubiquitous and extensive during formation of the definitive extrapericardial systemic and pulmonary pathways. In contrast, and as also acknowledged by the London group, a partially formed artery of the fifth pharyngeal arch has been identified in a solitary human embryo. In the developing mouse, however, there has been no instance in which, as far as we

are aware, it has been possible to identify either a segment of pharyngeal mesenchyme identifiable as a fifth arch, or a fifth pair of arch arteries. In about half of the embryos studied, nonetheless, both in our series⁷ and in an additional series⁸, collateral channels were identified at the insertion of the fourth and sixth arch arteries to the distal aorta. These findings, and those regarding remodeling of the aortic sac, offer alternative explanations for the lesions interpreted thus far as representing persistence of the arteries of the fifth pharyngeal arch. In this light, it is necessary to take note of the philosophical principle known as Occam's razor, or the law of parsimony. An excellent review of this principle is now provided by Wikipedia.⁹ With regard to medicine, we are informed that "A variation used in medicine is called the "Zebra": a doctor should reject an exotic medical diagnosis when a more commonplace explanation is more likely, derived from [Theodore Woodward](#)'s dictum "When you hear hoofbeats, think of horses not zebras".¹⁰ This is directly pertinent to the interpretations offered by the London group for their series of cases. In our opinion, better explanations can be offered on the basis of remodeling, and by invoking the law of parsimony, for the cases illustrated in their Figures 1 through 3 and 5. Thus, double barreled aorta is more likely to represent collateral channels. Most of the abnormalities of brachiocephalic arteries can well be due to extensive remodeling of the aortic sac. Aorto-pulmonary connections are as likely to represent remodeling of the arterial duct as persistence of the fifth arch artery. When taking probabilities into account, we speculate it is much more likely to be remodeling of the duct. As stated by Woodward, we should be thinking of horses, in other words remodeling of the aorta, its branches and the arterial duct, rather than zebras, represented by the fifth arch artery in the accompanying review.

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