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3D atlas of human embryology

New insights in human development

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CHAPTER 7 - SUMMARY

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"Our real teacher has been and still is the embryo, who is, incidentally, the only teacher who is always right."

Victor Hamburger (1900-2001)

This thesis starts with a scope and a general introduction on the embryonic period, the first eight weeks of human development (**chapter 1**). During this period, the approximately 0.1-0.2 mm fertilized egg, the zygote, develops into an embryo of less than 3 cm crown-rump length (CRL). Developmental biologists rank the embryos in 23 Carnegie stages according to the embryonic age that starts counting at fertilization. To compare embryonic age with the number of pregnancy weeks one needs to add two weeks to the embryonic age. This is because pregnancy weeks are normally counted from the first day of the last menstrual period. Two weeks after this day ovulation occurs, and when the egg is fertilized, embryonic development starts. The embryonic period encompasses significant growth and organogenesis and finishes after 60 days of development when the fetal period begins.

In **chapter 2.1** and **2.2** we present the *3D Atlas and Database of Human Embryology.* Based on stained histological sections we created a digital atlas with 14 interactive three-dimensional (3D) models of human embryology and a database encompassing 34 embryos covering the embryonic period between two and eight weeks of human development. Approximately 15,000 histological sections from the Carnegie Collection were analyzed by trained biomedical students under expert supervision, and up to 150 organs and structures per specimen were identified and digitally labeled. This is the first and most extensive digital 3D human embryology atlas, containing all developing organ systems.

The morphology presented in this atlas is directly connected to the original sections of the embryos in the Carnegie Collection—a connection that was in danger of being lost, with present-day textbook morphology becoming increasingly schematic and deviating from the original substrate. This atlas will therefore serve as an educational and reference resource for students, clinicians, and scientists interested in human development and development-related congenital diseases.

In **chapter 2.3** we focus on one of the embryos used for the 3D Atlas, the famous Heuser embryo. Comparing the Heuser embryo to two other stage 8 specimens from the Carnegie collection makes us doubt whether the Heuser specimen is representative enough to serve as reference model for this stage. It is worrying that most textbooks present an ever-changing succession of illustrations based on this single stage 8 specimen, often without proper referencing.

Most organ systems presented in our 3D Atlas perfectly resemble the descriptions and drawings of well-respected embryologists from decades ago. However, a number of detailed analyses of the development of the kidney, pharyngeal arch cartilages, and notochord show that the accepted descriptions of the development of these organs are based on comparative animal models rather than on factual observations in human specimens. These examples are elaborated in the following chapters.

In **chapter 3** the development of the most relevant axial structures; the notochord and the neural tube are highlighted. We show that the definitive notochord (**chapter 3.1**) is preceded in its development by the prechordal plate, notochordal plate and notochordal process. The notochordal process incorporates entirely into the endoderm, forming the epithelial notochordal plate, which acquires an "inverted U-shape", and remains intimately associated with the neural tube. Subsequently, the notochordal cells detach from the endoderm to form the definitive notochord, allowing the paired dorsal aortae to fuse between the notochord and the roof of the foregut. The descriptions in the modern textbooks resemble the notochord development in chicken embryos. In contrast to these descriptions, the formation of the definitive notochord in human starts in the middle of the embryo, and proceeds in both cranial and caudal directions.

Since the multi-site closure theory for neural tube closure was first proposed in 1991 as explanation for the preferential localizations of neural tube defects, the mechanism of closure of the neural tube has been a contentious topic. In **chapter 3.2** we observe that there is no evidence for more than one fusion site in human and mouse embryos. Therefore, we propose to reinstate the single-site closure theory for neural tube closure. We show that neural tube defects are not restricted to a specific preferential location, thereby refuting the reasoning underlying the multi-site closure theory.

In **chapter 4** the development of the urogenital system is highlighted. Human kidney development is generally described as to pass through three stages: pronephros, mesonephros and metanephros. The most striking difference between pronephros versus meso- and metanephros concerns nephron architecture. The pronephros comprises exclusively non-integrated nephrons with external glomeruli, whereas meso- and metanephros are composed of integrated nephrons with internal glomeruli. Non-integrated nephrons are not identified in histological sections of human embryos. Therefore, we conclude that a true pronephros is not present in developing humans. The most cranial part of the amniote excretory organ has often been confusingly referred to as pronephros. We recommend that the term pronephros should be avoided in amniotes unless all elements for a functional pronephros are undeniably present.

Chapter 4.2 focuses on the gonadal development. We state that, in contrast to the long-established theory on the descent of the gonads, gonads do not descend during the embryonic period. The indifferent gonads are longitudinally shaped organs that extend from the level of the fifth thoracic vertebra to the level of the fifth lumbar or first sacral vertebra around 40 days of development. Three weeks later in development, the cranial margin of the gonads can be found at the level of the second lumbar vertebra, while the caudal margin remains at the level it was at 40 days. This shows that the gonads become relatively shorter, giving the erroneous impression that they descend during embryonic development.

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Chapter 5 provides a new and relatively simpler theory on the development of the hyoid-larynx complex, to facilitate better understanding of the etiology of anatomical variants. We observe that the development of the hyoid-larynx complex in human embryos (**chapter 5.1**) is less complicated than it is currently described in textbooks. The body of the hyoid bone originates from a single growth center, without overt contributions from second and third pharyngeal arch cartilages. The fourth and sixth arch cartilages are not detected in human embryos; the thyroid and cricoid cartilages develop as mesenchymal condensations in the neck region unrelated to the arch cartilages.

In **chapter 5.2** we give an overview of the anatomical variants of this highly polymorphic hyoid-larynx complex. Apart from minor variations like age-dependent ankylosis of the hyoid and presence of triticeal cartilages in the lateral thyrohyoid ligament, most variants are found in the trajectory of the second pharyngeal arch cartilage. We suggest to consider Eagle's syndrome and the aberrant hyoid apparatus as two expressions of one entity, preferably referred to as 'second pharyngeal arch cartilage anomalies'. As some variants mimic a fracture of the hyoid-larynx complex, we emphasize the importance of our work for forensic experts.

In **chapter 6** we present a hitherto unprecedented detailed description of muscle anatomy in an 8 weeks old embryo, in topographic relation with the skeletal and peripheral nervous systems. Almost all adult skeletal muscles of the trunk and limbs are individually identified in their relative adult position. Although the muscular system is an often neglected or only generically described topic in embryology textbooks, some interesting findings are described. The pectoralis major muscle, for example, is divided in three separate muscle heads whereas in adults it is known as a single large muscle. The 3D reconstructions show remarkable highly developed extraocular, infrahyoid and suprahyoid muscles at this age but surprisingly also absence of the facial muscles that have been described to be already present at this stage of development.

In **chapter 7** & **8** the thesis is summarized in English and Dutch and future perspectives are discussed.

Chapter 9, provided as addendum, contains two examples of the use of the 3D Atlas in clinical settings as well as in education. **Chapter 9.1** presents ultrasound image-rendering software that allows the visualization of the entire fetal cerebral ventricular system in a completely new way. This software enables imaging of structures not usually seen using standard 2-dimensional or 3D methods and enables identification and diagnosis of fetal central nervous system abnormalities well before the second trimester. In **chapter 9.2** we show that the 3D Atlas has proven to be a valuable resource, in addition to the existing resources, to teach the intricate developmental processes of human embryology to biomedical students, especially in a blended learning curriculum.

Future perspectives

The findings described in chapters 2 to 6 illustrate the gaps in our knowledge in human embryology and therefore in the manifestations and the causes of birth defects. The focus of this thesis lies mainly on the period of organogenesis, between embryonic weeks 3 and 8. Although most organs are formed after eight weeks of development, the majority has not yet assumed their final location and proportion when compared to a full-term neonate, whereas e.g. the genital system is even far from complete at the end of the embryonic period. We are grateful to the Board of Directors of the AMC and to the Graduate School for providing funding for the establishment of the *3D Atlas of Fetal Development* which enables us to continue our research. Our main mission is to provide clinicians with true-to-nature (digital) 3D models of fetal human development that can be used as reference models on which advanced software on ultrasound machines can base their fetal proportions and volume-rendering algorithms. By this, we hope to contribute to the earlier diagnosis of congenital abnormalities.

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