3D atlas of human embryology

New insights in human development

de Bakker, B.S.

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Chapter 1.2 - General Introduction

Bernadette S de Bakker

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"All truth passes through three stages.
First, it is ridiculed.
Second, it is violently opposed.
Third, it is accepted as being self-evident."

Arthur Schopenhauer, (1788-1860)

The human embryonic period is internationally defined as the first eight weeks of development, counted from the time of conception (Streeter 1942; Streeter 1945, 1948; Streeter 1949; Streeter 1951; O'Rahilly and Müller 1987). Although the arrangement of organs in the body is laid down during this period (de Bakker et al. 2016), not all organs are fully developed after eight weeks, when the developing human enters the fetal phase. The first eight weeks of development can be divided into three distinct periods. The first period starts with the fertilization and runs until implantation. The second period covers the implantation phase and ends by the formation of the three-layered germ disc. The third embryonic period encompasses significant growth and organogenesis and finishes when the fetal period begins officially after 60 days of development (O'Rahilly and Müller 1987). The first two embryonic periods will be briefly discussed, after which the period of organogenesis and embryonic growth will be highlighted.

During the first period (day 1-6), the fertilized egg cell or zygote becomes a morula through the process of cleavage, after which compaction of the thus cleavaged cells leads to the division between embryoblast (or inner cell mass, from which the embryo and amnion will form) and trophoblast (or outer cell mass, from which the placenta and chorion will be derived). By the process of cavitation, the blastocyst cavity arises and the morula is now called a blastocyst. When the blastocyst hatches from its protective shield, the zona pellucida, it is able to invade the epithelium of the uterus endometrium to implant at day 7.

In the second period (day 7-19) the embryonic pole of the implanted blastocyst (embryoblast) measures less than 0.5 mm in size and forms the amniotic cavity, the epiblast and the hypoblast. The hypoblast delimits the yolk sac on the ventral side of the embryo and the epiblast proper is the sole germ layer from which all embryonic organs will later derive. By the process of gastrulation, the epiblast first forms the extra-embryonic mesoderm, to provide in the embryos protection and nurture, and subsequently the endoderm, intra-embryonic mesoderm and ectodermal layers are formed. The embryo exists now of a three-layered germ disc and measures 0.6 mm at day 19.

The third period of embryonic development (20-60 days) encompasses organogenesis and significant growth. In this period, the embryo grows exponentially; its volume increases with 25% per day and reaches a total volume of 2790 mm3 at 60 days of development (**Fig. 1**) (de Bakker et al. 2016). Interestingly, there are substantial differences among the growth rates of independent organs.

With the advancement of ultrasound techniques, enabling clinicians to monitor pregnancies in the early first trimester, it is increasingly relevant to know the volumes of independent organs throughout the stages of embryonic development. The *3D Atlas and Database of Human Embryology* allows to quantify relative growth between 60 independent organs at 34 time points during embryonic development (de Bakker et al. 2016). The neural tube, the precursor of the brain and spinal cord, accounts for a constant relative volume of ~10% of the total volume of the embryo. The liver on the contrary, increases fast in volume between day 21 and 33, after which it also reaches a steady relative volume of 8%. The relative volume of the notochord, the vertebral precursor, decreases exponentially during embryonic growth, whereas the relative volume of the kidney increases exponentially after its first appearance.

Another aspect of embryonic growth involves rather vague terminology as 'relative growth differences' and 'migration' of organs. It has long been thought that the kidneys migrate in cranial direction during development. A clinical example is the horseshoe kidney, an anatomical variation with an incidence of one in 500 adults (Glodny et al. 2009; Taghavi, Kirkpatrick, and Mirjalili 2016). The etiology of the typical shape of the fused kidneys has always been explained as that the fused kidney encounters the inferior mesenteric artery during ascent, thereby assuming the shape of the horseshoe as it extends around it. Thanks to the latest 3D reconstruction and measurement techniques (de Bakker et al. 2016) we now know that the kidneys do not ascend during embryonic development, but that the inferior mesenteric artery "descends" from the first to the third lumbar vertebra, giving the erroneous impression that the kidneys ascend.

Eight weeks after conception the crown-rump length of the embryo is 3 cm and from now on it is dubbed a fetus. But, since the urogenital and nervous systems among others are still in the process of development at this point, it is simplistic to state that all organs are completed after the embryonic period and that the fetus only has to grow and ripen to reach term age. Further research is needed to quantitatively study individual organ growth in the early fetal period.

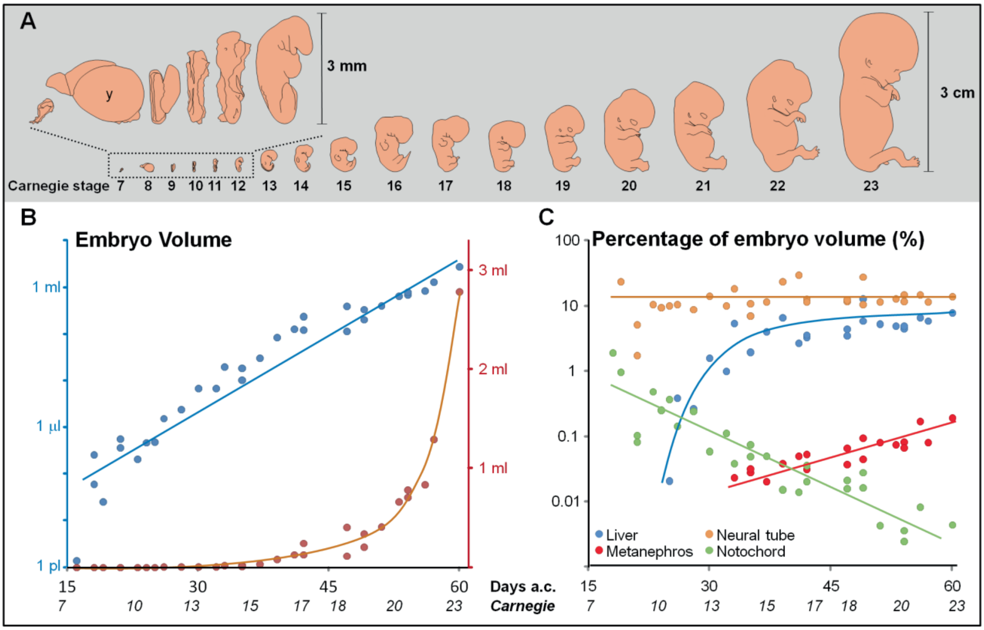

Fig. 1. Growth of the human embryo during the first 2 months of development. From B. S. de Bakker et al., Science (2016) (de Bakker et al. 2016). Reprinted with permission from AAAS. **A** Length of the embryo between Carnegie stages 7 and 23. Stages 7 to 12 are enlarged. Note the large round yolk sac (y) in stage 8. Drawings (left to right) are of specimens 8752, 8671, H712, 6330, 6784, 8505A, 0836, 8314, 3512, 6517, 8521, 8524, 2114, 462, 7258, 895, and 9226 from the Carnegie collection of the Human Developmental Anatomy Center at the National Museum of Health and Medicine in Silver Spring, MD, USA. **B** Increase in body volume with respect to days after conception (days a.c.) and Carnegie stages (x axis). Embryo volumes are plotted on a logarithmic scale (left y axis; blue dots) and on a linear scale (right y axis; red dots). The linear relation between log(volume) and days of development indicates a constant growth rate of the embryos in this development period. **C** Relative volume of organs as percentage of embryonic volume (y axis) with respect to days after conception and Carnegie stages (x axis). Neural tube (not including the neural canal), liver, metanephros, and notochord are shown as examples (see de Bakker et al. 2016 for other organs). The neural tube accounts for a constant relative volume of ~10% of the total volume, whereas the relative volume of the liver first increases, after which it also reaches a steady relative volume of 8%. The relative volume of the notochord decreases exponentially, whereas the relative volume of the metanephros increases exponentially after its first appearance.

1.2

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