Editorial

EMBRYOLOGY TEACHING: AN OFTEN-NEGLECTED PART OF THE MEDICAL CURRICULUM

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Embryology is a science of the origin and development of living organisms. The study of human embryology has theoretical (as a pre-clinical course during medical study), but also important clinical significance. Embryology is a fascinating field of science which can guide students of medicine or natural sciences in a miraculous way through the laws of human development from fertilization to birth. Owing to embryology, we get to know ourselves because we all went through this period of development (although we do not remember it). This issue will again capture our attention or has already done it in time when we are about to become parents or grandparents, and we will be interested in the development of our children or grandchildren. Regarding medical studies, embryology facilitates the study of anatomy as it can also explain the emergence of anatomical variations, anomalies. The knowledge of embryology is also beneficial for medical students in the preparation for the exam in Gynecology and Obstetrics (infertility disorders and assisted reproduction techniques, structure and function of the placenta, the factors affecting the development of the embryo), as well as in Pediatrics and Surgery (problems of congenital developmental defects and anatomical variations).

Historical Introduction

Intrauterine development has fascinated mankind since time immemorial. In the beginning, there were mainly religious reasons that forced scientists to think about when a new human life starts. An ancient Greek philosopher Aristotle (384-322 B.C.) predicted that a developing individual does not have its own soul in the early stages of development (*fetus inanimatus*, unsouled fetus). At the beginning of development, it has only a vegetative and later animal soul, and it is, therefore, similar to plants and lower animals. He was based on his theory of epigenesis in which single organs of an individual develop from a simpler to more complex form. With some modifications, the concept of delayed ensoulment - at 40 or 90 days after fertilization - was adopted for example by Saint Thomas Aquinas and remained valid throughout centuries (Obladen, 2017). Basic processes that today we refer to as fertilization and subsequent early development were previously ambiguous (it was a period without a quality light microscope). On the one hand, there was Aristotelian theory of epigenesis, i.e. the theory of gradual evolution of individual organs. On the other hand, there was formed the theory of preformationism under which the already finished miniature organism was hiding inside the germ cells. There were two competing models of preformationism: ovism and spermism (animalculism). According to ovists, a woman's oocyte is the essence of a new individual, whereas the sperm only serves to start the developmental process. The father of ovist preformationism is an English physiologist William Harvey (1578-1657) who asserted "*omne vivum ex ovo*" (all life begins from an egg). In contrast, there were animalculists, e.g. the inventor of the light microscope Dutchman Antony van Leeuwenhoek. Leeuwenhoek (1632-1723) together with his colleague Ham first observed by light microscopy sperm and believed they saw in its head a preformed human being (so-called *homunculus*). Primitive preformed opinions were revised in the 18^{th} century by a German-Russian physiologist and one of the founders of embryology Caspar Friedrich Wolff (1733-1794). Wolff in his dissertation "*Theoria Generationis*" revived and supported Aristotle's theory of epigenesis. He assumed that the gradual development of an individual is controlled by a kind of "*vis essentialis*", i.e. life or formative force (Van Speybroeck et al., 2002).

Embryology as a modern science began to develop after the discovery of a light microscope. Thanks to the development of microscopic techniques, a German-Latvian biologist Heinz C. Pander (1794-1865) managed to describe the three germ layers in the chick embryo. The presence of germ layers also in other animal species was confirmed by an Estonian scientist Karl Ernst von Baer (1792-1876). In 1842, Von Baer formulated the basic laws of embryogenesis, including for example a postulate that the general structural relations are likewise formed before the most specific appear (e.g. the skin has in embryogenesis the equal basis in all vertebrates, and only later there are formed scales, feathers, or hair).Von Baer laws were the basis also for publishing the work of an English biologist Charles Darwin (1809-1882), entitled "*On the Origin of Species*" (1859). Darwin's theory of evolution influenced many scientists, such as a German biologist Ernst Haeckel (1834-1919). His work "Anthropogenie" (1874) is often considered as one of the first textbooks of embryology.

This historical overview also shows that embryology has always been at the center of concerns of physicians and natural scientists. But what is the current status of embryology at medical schools? There are several reasons why embryology is an appropriate component of the standard medical curriculum. These reasons are equally important, so their order is more or less random.

1. Embryology as Part of Biological Sciences

Embryology provides evidence for the development of man as a result of the evolution of the animal kingdom. Embryonic development of man is a condensed and abbreviated repetition of the continued gradual evolutionary development of the whole subphylum of vertebrates, even the entire animal kingdom. Vertebrates resemble each other in the early stages of embryonic development and differences appear along with their gradual embryonic development. This rule was first noticed by Ernst Haeckel, and he named it as the recapitulation theory, or biogenetic law (ontogeny recapitulates phylogeny) (Olsson et al., 2017). Even in the development of man, there could find many examples that confirm Haeckel's hypothesis. We cite the following examples:

- the presence of branchial (pharyngeal) arches on the cranial end of the embryo during the 4th and 5th week of development that resemble gills of aquatic animals
- the gradual emergence of all stages of kidney development (pronephros, mesonephros, and metanephros) also in humans, while some were characteristic only for fish or amphibian
- the development of the cloaca as the common end portion of the digestive and urogenital system, typical of the class of animals from fishes to birds
- the morphology of the developing heart also reminds the heart of particular classes of animals (the embryonic heart tube with its inflow and outflow portion is similar to the heart of fishes, etc.)
- the formation of somites reminds segmented body structure (segmentation) of some invertebrates and vertebrates
- the hematopoietic function of the liver and spleen during the intrauterine development reminds the function of these organs in those animals (fish and amphibian larvae) that have no bone marrow yet

At this point, I would like to remind the words of a giant of Czech embryology, Professor Jaroslav Slipka, MD, DSc. (1926-2013): "Every tissue or organ has their own history. History has two faces - ontogenesis and phylogenesis. Both are equally important."

2. Relevance of Embryology to the Study of Anatomy

Another important function of embryology is to provide a logical basis for understanding the overall organization of the human body. Embryology describes the development of the body organs of the adult and explains the emergence of possible variations in their number, changes to final position or topographic particularities of human anatomy (variant anatomy). The variant anatomy is a specific large subfield of gross anatomy. Anomalies of the human body which are not considered as serious defects of the development that means they do not impair the function are considered as variants (Kachlik et al., 2016). Especially in the areas of surgery and radiology, it is important to think about the possible anatomical variations, and therefore it is important to understand the laws of embryology for each clinical discipline.

3. Relevance of Embryology to Prenatal Diagnosis

Modern embryology deals not only with morphogenesis - the development of organs but also with various developmental disorders that result in birth defects (congenital anomalies). First and foremost, an obstetrician and pediatrician should be thoroughly familiar with the human development before birth. Every doctor encounters congenital anomalies in their practice. A precondition for recognizing birth defects, understanding their formation during development and often a successful treatment is the understanding of the normal development of man before birth. Improving the methods of prenatal diagnosis (amniocentesis, ultrasound, fetoscopy, biochemical screening or analysis of free fetal DNA from maternal blood) allows early detection of many birth defects, identify their causes and by novel operating procedures, it is sometimes possible also to remove the consequences (Rink and Norton, 2016; Van den Veyver, 2016). To date, there has been a range of developmental anomalies that can be corrected during the fetal period in the uterus (so-called fetal surgery). In fact, the wounds after such surgery heal much better *in utero*; however, the development of fetal surgery is still limited by financial, technical, and professional demands of the performance and by a high risk for subsequent preterm delivery (because the human amnion does not heal, leading to a significant incidence of premature rupture of the membranes) (Kitagawa and Pringle, 2017). In the future, there might also be possible the correction of the identified chromosomal fetal anomalies (gene therapy), or there will be more extended also a replacement therapy with the administration of products of defective genes (e.g. enzyme replacement therapy).

1.	Susceptibility to teratogenesis depends on the genotype of the conceptus and a manner in which this interacts with adverse environmental factors.
2.	Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to an adverse influence.
3.	Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate sequences of abnormal developmental events (pathogenesis).
4.	The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.
5.	The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent).
6.	Manifestations of deviant development increase in frequency and degree as dosage increases from the no-effect to the totally lethal level.

Table 1. Wilson's Six Principles of Teratology Reviewed by Friedman (2010)

4. Embryology and Understanding of Congenital Anomalies

A scientific discipline teratology (from Greek *teratos* - monster, malformation) deals with the causes of congenital defects. It is important to know harmful teratogenic factors and their effects on the developing organism at certain periods to produce healthy offspring. On the other hand, nowadays, there is already evidence of the embryo-protective effect of certain vitamins (such as folic acid) whose intake in natural form is not usually sufficient. The principles of teratology were published in 1959 by James G. Wilson (1915-1987). He expanded the original five principles in 1977 to six (Table 1). Teratology uses the methods of experimental embryology (based on animal models), develops test methods for embryo-toxicity on tissue cultures and aids to discover the causes of serious developmental malformations. Over the past 50 years, the Teratology Society (USA) has also developed the scientific basis to prevent birth defects caused by rubella and alcoholism, as well as other prenatal exposures (Shepard et al., 2010).

5. Clinical Embryology and Reproductive Medicine

With the development of methods of reproductive medicine, there specifically developed also a new laboratory discipline, clinical embryology. Assisted reproduction is a medical discipline that deals with oocytes, sperm and embryos outside the body *(in vitro)* aimed at a woman to get pregnant (infertility treatment). Currently, the field of reproductive medicine includes also the issues of freezing of gametes and embryos (cryopreservation), as well as genetic analysis of embryonal cells (blastomeres) before its transfer into the uterine cavity. The birth of the world's first "test tube baby" in 1978 significantly contributed to the development of clinical embryology. Both a British gynecologist Patrick Steptoe (1913-1988) and a physiologist Sir Robert Edwards (1925-2013) took credit for developing methods of *in vitro* fertilization. A clinical embryologist is a close co-worker to a gynecologist. Embryologists in the centers of reproductive medicine, among other activities, are responsible for the examination of the ejaculate and semen analysis (spermiology), for the course of *in vitro* fertilization (e.g. using micromanipulation techniques), for evaluation of adequacy of the early embryonic development and in the case of pre-implantation genetic screening for taking the daughter cells (blastomeres) from the morula. Following relevant training and exams, clinical embryologists can obtain an internationally recognized certificate from the European Society of Human Reproduction and Embryology (Kovacic et al., 2015).

6. Modern Trends in Embryology, "Molecular Embryology" and Regenerative Medicine

As another application of embryological knowledge into clinical practice can also be regarded the study of knowledge of regeneration and reparation mechanisms. In fact, these mechanisms are at the molecular level often similar to activities which take place during embryonic development. For example, signaling pathways responsible for the formation of new blood vessels during embryonic development also apply during tissue regeneration and remodeling in the postnatal period, as well as in the formation of new blood vessels in tumors (Kyselovič and Varga, 2017). Similarly, without the knowledge of genes and signaling molecules of the migration of neural crest-derived cells during embryogenesis, it is not possible to understand the concomitant occurrence of large intestine motility disorders (e.g. Hirschsprung disease) with congenital defects of the urinary system and the heart (Slavikova et al., 2015).

Quo Vadis Embryology Teaching?

This overview also shows that embryology is not a closed static field with a set of stable and unchangeable knowledge. Embryology is growing by the development of biological sciences, like all branches of medicine, and must, therefore, respond to ever increasing range of knowledge also in the curriculum. Today, modern embryology examines the development of man from the macroscopic description up to gene expression. Knowing the roles of signaling molecules and transcription factors has allowed better understanding of the mechanism of processes during the development and the origin of congenital anomalies. However, in the curricula of medical schools, there is often larger space for other courses such as molecular biology, immunology, biochemistry, and often at the expense of morphological sciences (Grim, 2009).
Embryology teaching varies considerably not only between countries but also between different universities (Moxham et al., 2016). For instance, in the USA, embryology is usually taught together with gross anatomy (integrated courses) (Drake et al., 2002), while in most medical schools in Slovakia or the Czech Republic it is taught in conjunction with histology. Alternatively, there are curricula in which it is a completely separate stand-alone course. In general, we can say that recently there has been observed a trend of reducing the number of hours devoted to embryology, including laboratory hours in embryology courses (Drake et al. 2009). If embryology is taught only in the lower years of medical studies, students often poorly understand and underestimate the clinical importance of this scientific field. It is, therefore, desirable to add to the curriculum also lectures on "clinically oriented embryology" in later years of the medical program (Scott et al., 2013; Hamilton and Carachi, 2014).
Based on my opinion, very useful and high-quality recommendations for a core syllabus for the embryology teaching were published by Fakoya et al. (2017). The question is: how can be embryologic information presented effectively to medical students? Different curricular models in embryology teaching exist, but at most medical schools, embryology is presented as a lecture-based course, typically with no laboratory (Carlson, 2002). Adequate textbooks and computer-based learning programs are extremely helpful in teaching. The advantage is when they contain test questions for final verification of

knowledge or problem-based model situations in the context of the clinical problems. Some authors (e.g. Nieder et al., 2005; Vasan et al., 2008; Shankar and Roopa, 2009) recommend "team-based learning" (independent out-class preparation for in-class discussion in small groups). More than 80% of students agree that team-based learning is helpful to their learning.
In conclusion, it is to be hoped that embryology, either as part of other courses or as a stand-alone course, will not cease to exist at medical schools. And future physicians worldwide will still receive information on this "pillar" of under-graduate medical courses with a significant impact on clinical practice.

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