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Early Embryonic Development: A Contemporary Interpretive Reading of Ibn Sina's Book of Animals (*Kitab al- Hayawan*) A Quick Closer Look at Ibn Sina's Scientific Heritage

Magdy Mohamed Zaabal[1*], Wahid Mohamed Ahmed[1], Hesham H. Elkhadrawy[1] and Faragalla M. El Moghazy[2]

[1]*Department of Animal Reproduction and Artificial Insemination, Veterinary Research Institute, National Research Centre, Dokki, Giza, Egypt*

[2]*Department of Parasitology and Animal Diseases, Veterinary Research Institute, National Research Centre, Dokki, Giza, Egypt*

[*]Corresponding Author
Magdy Mohamed Zaabal, Department of Animal Reproduction and Artificial Insemination, Veterinary Research Institute, National Research Centre, Dokki, Giza, Egypt.

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Abstract

The term embryonic development first appeared in Aristotle's book "Generation of Animals "and for this reason, he rightfully deserves to be considered the first developmental biologist. In the 19th century, Karl Ernst von Baer (1792-1876) developed modern embryology through his discovery of the blastula stage of development and the notochord and became the first person to observe a human egg. Ibn Sina's encyclopedic work "The Cure" (ash-Shifaa), the book, renowned as the greatest encyclopedic work in philosophy, comprises three major sections: logic, natural sciences "physics and biology", and theology. In the second section, Ibn Sina dedicated a unique book entitled: "Book of Animals (Kitab al- Hyawan), in which he explained the basic analysis of early embryonic development and concluded that the change from semen to animal takes place through a series of substantial alterations. The current article represents an effective and logical intersection between more than one scientific, philosophical, and religious field. On one hand, it belongs to the philosophy of science and also the history of biology, while philosophy and genetics combine to formulate this unique scientific content of the theory of embryonic development in two eras separated by more than ten centuries. In this article, we reviewed Ibn Sina's view of the embryonic development through the alterations (transformation of the matter of fetus (janin) up to its completion. Ibn Sina based his view on two main sources; one of them is a reliable and widely circulated source, namely the Holy Qur'an, for example (Surah Al-Hajj, (The Pilgrimage) No.22/17, verse 5). The second source, is hidden in Ibn Sina's mind and consciousness, it is his unique intuition that enabled him to see things that others could not. Ibn Sina proved that the process of embryonic development is a qualitative, creative and substantial alteration (transformation), not merely gradual changes.

Keywords: Ibn Sina, Embryonic Development, Substantial Alterations, Divine Creation, Embryology

1. Introduction

Ibn Sina is not only an outstanding philosopher but also, he is a brilliant biological pioneer. Ibn Sina's encyclopedic work "The Cure" (ash-Shifaa), the book, renowned as the greatest encyclopedic work in philosophy, comprises three major sections: logic, natural sciences "physics and biology", and theology. In the second section, Ibn Sina dedicated a unique book entitled "The Book of Animals (*Kitab al- Hyawan*), in which he explained the basic analysis of early embryonic development and concluded that the change from semen to animal takes place through a series of substantial alterations.

Fertilization process leads to five critical cellular developments, which are, the completion of meiosis II within the female gamete is directed by calcium-induced activation of the anaphase-promoting complex. The determination of chromosomal sex is now complete. The sperm entry point may localize polarity to the determination of early axis formation. Then finally, there is an initiation of the cleavage of the zygote [1].

The zygote is the beginning of life. Because, in short, it represents the early embryonic development process, in which it undergoes several successive stages of cleavage to increase cell numbers and then forms a blastocyst, while at the same time the embryo gets rid of maternal and paternal influences to start its own life with its own genetic material [2].

During the first three weeks, teratogens have an all or nothing effect on the embryo. During the third through eighth-week growth and function are affected. Weeks nine to thirty-seven are known as the fetal period. This period is important for extensive growth in size and continuous differentiation of organ systems [3].

Early embryonic development must complete two processes. The first is to complete the maternal-to-zygotic transition (MZT) the zygote is thus freed from maternal influence, ensuring that subsequent embryonic development is solely controlled by the zygote's genome. The second process is to make two consecutive cell fate choices. After that, the embryo differentiates into three lineages, including the epiblast (Epi), which will develop into embryonic tissues, and the trophectoderm (TE) and primitive endoderm (PrE) that will develop into extra-embryonic tissues. The two processes are regulated by complex molecular networks, and in this section, we will review the known molecular mechanism of early embryonic development [4].

Large amounts of transcripts and proteins are produced and stored in oocytes, and prior to ZGA the embryo is dependent on these maternal factors. Maternal effect genes (MEGs) are a class of genes that are transcribed in oocytes and are essential for oocyte maturation, fertilization, and early embryonic development. *Mater* (or *Nlrp5*) was the first reported mammalian MEG, discovered in 2000, and since then about 80 genes have been reported to be MEGs. All of these genes are important for female fertility as confirmed in humans or in mouse models [5].

Embryogenesis depends on a highly coordinated cascade of genetically encoded events. In animals, maternal factors contributed by the egg cytoplasm initially control development, whereas the zygotic nuclear genome is quiescent. Subsequently, the genome is activated, embryonic gene products are mobilized, and maternal factors are cleared. This transfer of developmental control is called the maternal-to-zygotic transition (MZT) [6]. Furthermore, early embryonic development is regulated epigenetically. During the development process, the epigenetic signature changes as the cell enters fertilization and/or differentiation. DNA methylation is an important epigenetic event, regulating gene expression and chromatin structure in any developmental processes including gene imprinting and embryogenesis [7].

2. Material and Methods

2.1. Original text of Ibn Sina in Arabic (Appendix 1)

2.2. Translation of Ibn Sina's Text

The Cure (ash-Shif[a])
The Book of Animal
Ninth article, chapter No. 5

Alteration of the Matter of the Fetus (*janin*) up to it is Completion [8].

The first state is the churning (*zabadiya*) of the semen, which is the actuality of the formal power 'imagined power/faculty' (i.e. the imagined sexual ability, which is the "latent power' according to Ibn Sina) [9].

The next state is the manifestation of the drop of blood in the uterine wall [or endometrium], and its continued dilation in the uterine wall. The third state is the alteration of the semen into a blood clot and after [this alteration], its alteration into a lump of flesh (*mudgha*). Afterwards is its alteration leading to the generation of the heart and primary organs, as well as its blood vessels, which is followed by the generation of the extremities [or limbs]. For each alteration, or two together, there is a period of time where [the developing thing] remains at rest in [that state].

This is not something that is undisputed (there is no disagreement about it), however, it differs between males and females, and it is slower in females (meaning that the difference is in the duration of each stage, for example, if the fetus is male or female).

Those with experience and testing have opinions on this matter, and there is no real disagreement among them. Each of them judged based on what he encountered in his testing (experience) and it is not impossible that what the other tested was actually something contrary to his. However, all of that is undoubtedly the majority, and the majority is in the one in whom the most is born (meaning that there is no real disagreement among experts except to the extent of practical experience in generation, and in any case, the majority opinion will be that of the one with the broadest experience).

The foaming stage lasts six days, and the appearance of red lines and spots begins three days later. This makes nine days from the start, though it may be one day earlier or later. Then, after another six days, the fifteenth day of the gestation period (the formation of the leech), the blood flow penetrates the entire embryo, and it becomes a leech. It might be a day or two earlier or later, and then after twelve days it becomes flesh. The flesh pieces have become distinct, and the three organs (perhaps referring to the heart, liver, and brain) have become differentiated, and the marrow moisture has spread, perhaps two or three days later or later (advanced). Then, after nine days, the head separates from the shoulders.

The limbs are distinct from the ribs and abdomen, a distinction that is felt in some and not felt in others, until it is felt four days later, or the completion of forty days. In rare cases, it is delayed to forty-five days, and in the rarest cases, it is thirty days. It was mentioned in the first lesson that if a stillborn fetus after forty days is cut open and placed in cold water, a small, distinct object will emerge. Males develop faster than females in all of this, and it is generally (approximately) that the shortest period of conception for males is thirty days. As for determining the sex of the fetus (male or female) within the details of the gestation period, this is a matter that some doctors treat with recklessness and risk.

The first thing the sperm finds is to breathe, and the first thing the imaging process does is activate the natural, primal heat. Then the esophageal and periphery processes begin, and then the gaseous system takes over. Some believe that the fetus may breathe through its mouth, and even that it breathes most of its breath through the mouth if it is conceived in the womb; however, there is no evidence for this. Others believe that when the fetus reaches its full development (formation/formation), it is twice as large as it was initially conceived (twice as it was intended to be).

Movement occurs (in some cases, the fetus's size relative to the gestational age is almost double what we imagined or estimated, causing it to move); and if twice the amount of time it has moved, birth occurs (and if the time since its first movement is nearly double the amount, birth occurs). Milk production occurs with the fetus's movement. It has been said that. The average gestation period is thirty-five days, so the fetus moves in seventy days and is born in two hundred and ten days, which is seven months. If it is longer, it is forty-five days (and at most, fetal movement may increase from the beginning by ten days, making it forty-five days). It moves in ninety days and is born in two hundred and seventy days, for nine months; and this is something in which the compiler does not establish a judgment (that is, in the end these estimates may not be final or conclusive but relative in all circumstances). * (Between the brackets: author's explanation and interpretation).

3. A Detailed and Sophisticated Formulation of Ibn Sina's Ancient Theory From Modern Embryological Perspective (Secular Approach)

A thousand years after Ibn Sina formulated his unique theory of embryonic development, and thanks to scientific and technological contemporary advancements, we now have a sufficient amount of accurate, detailed, and illuminating information about embryology and its vast and exciting world. Despite this remarkable and compelling development, Ibn Sina's initial contribution will remain a shining beacon throughout the centuries thanks to his unique scientific intuition. In the following lines, we will present, from a bird's-eye view, the main features of this contemporary scientific development in embryology.

Fertilization occurs when a mature male gamete fuses with female gamete, both of them contains 23 chromosomes (haploid cell) forming a zygote, which is diploid cell with 23 pairs of chromosomes (46 chromosomes). This zygote is formed approximately 24 hours after fertilization. Fertilization usually occurs in the ampullary part of the fallopian (uterine) tube [10,1].

Therefore, the three days, the zygote undergoes rapid cell division without cell growth, a process called cleavage. In human embryonic development at the eight-cell stage, having undergone three cleavages the embryo starts to change shape as it develops into a morula and then a blastocyst. At the eight-cell stage the blastomeres are initially round and only loosely adhered. With further division in the process of compaction the cells flatten onto one another [12].

At the 16–cell stage the compacted embryo is called a morula. At the 16-cell stage, the morula enters the uterus and the process of compaction occurs, as a result of which individual blastomeres become less distinct [13].

The morula is now watertight, to contain the fluid that the cells will later pump into the embryo to transform it into the blastocyst [14,15].

A blastocyst is a cluster of dividing cells produced by a fertilized egg. It possesses an inner cell mass (ICM) also known as the embryoblast which subsequently forms the embryo, and an outer layer of trophoblast cells called the trophectoderm. This layer surrounds the inner cell mass and a fluid-filled cavity or lumen known as the blastocoel. In the late blastocyst, the trophectoderm is known as trophoblast that gives rise to the chorion and amnion, the two fetal membranes that surround the embryo [16-18].

The blastocyst moves into the uterus and attaches to the endometrial lining, a process known as implantation. This stage is crucial as it allows the fetus to receive nutrients from the mother. Implantation is the process of the blastocyst embedding into the endometrial lining of the uterus, which typically occurs in Week 2 of development [19].

In the following week, the cell mass divides and forms a bilaminar disc. One layer will develop into the embryo, while the other, forms the yolk sac. Every step in the gestational period is crucially orchestrated to ensure appropriate development of the embryo. The embryonic disc and cavities are enclosed by the chorionic membrane within the chorionic cavity.

Gastrulation marks the formation of the three germ layers in the embryonic disc: endoderm, mesoderm and ectoderm ach of which will develop into different organs and systems in the body. Early in development at the time of gastrulation a small group of cells are "put aside" to later form oocytes and spermatozoa, these cells described as the primordial germ cells (PGCs) [20].

Following fertilization, the nervous system begins to form in the 3rd week of development. At the end of week two, a structure called the primitive streak appears as a groove in the epiblast layer of the bilaminar disk. Cells within the epiblast migrate downward through the primitive streak, giving rise to three

layers from the initial two. These three germinal layers form the trilaminar embryonic disk: Endoderm, innermost layer. Mesoderm, middle layer, and Ectoderm outermost layer. The nervous system is derived from the ectoderm, which is the outermost layer of the embryonic disc. For more details, check out our article on early embryonic development [21].

In the fourth week, heart folds begin to develop and beat. Structures for ears and eyes also start forming. The heart derives from embryonic mesodermal germ layer cells that differentiate after gastrulation into mesothelium, endothelium, and myocardium [22].

The heart tube continues stretching and by day 23, in a process called morphogenesis, cardiac looping begins. The cephalic portion curves in a frontal clockwise direction. This curved shape approaches the heart and finishes its growth on day 28. This time no septum is present in heart [23].

In the middle of the fourth week, the sinus venosus receives venous blood from the poles of right and left sinus. Each pole receives blood from three major veins: the vitelline vein, the umbilical vein and the common cardinal vein [24].

At the end of the fourth week, two atrioventricular endocardial cushions appear. Initially the atrioventricular canal gives access to the primitive left ventricle, and is separated from arterial bulb by the edge of the ventricular bulb. In the fifth week, the posterior end terminates in the center part of the upper endocardial cushion [25].

On day 34, the brain begins to differentiate into the forebrain, midbrain, and hindbrain. This process involves rapid growth in neural cells, critical for cognitive development. In early development (before birth and during the first few months), the brain undergoes more changes in size, shape and structure than at any other time in life [26].

4. Early Embryonic Development According to the Holy Quranic Revelation (Divine Approach)

4.1. Excerpts from the Verses of the Holy Qur'an Explaining the Meaning and Role of Germ Cell "*Al-Nutfah*"

- Surah Al-Mu'minun (The Believers) No.23/18, verses13 and 14: In the name of God, the Most Gracious, and the Most Merciful {We created man of a lineage/strain of clay. Then, We made him as a "*Nutfah*" (sperm) in a safe, firmed lodging.[13] Then, We made the "*Nutfah* "into a clot (coagulated drop of blood), then we made the clot into a little lump of flesh, then We made out of that little lump of flesh bones, then We covered (clothed) the bones with flesh, and then We brought it forth an another creation. So, Blessed Allah, the best of creators.[14]
- Surah Al-Hajj, (The Pilgrimage) No.22/17, and verse, 5: In the name of God, the Most Gracious, and the Most Merciful {O mankind! If you are in doubt about the Resurrection, verily We have created you from dust, then from a *Nutfah* (germ cell) then, from clot (a piece of thick coagulated blood), then, a little lump of flesh- some formed and some unformed (as in the case of miscarriage) - that We may (it) clear to you (i.e. to show you Our Power and Ability to do what We will). And We cause whom We will to remain in the wombs for an appointed term
- Surah Fatir, (The originator of Creation or The Angels) No.35/22, verse 11: In the name of God, the Most Gracious, and the Most Merciful {And Allah did create you (Adam/ mankind) from dust, then from "*Nutfah*", and then He made you pairs (male and female). And no female conceive or gives birth but without His knowledge. And no aged man is granted a length of life nor is a part cut off from this life (or another man's life), but is in the Book (*Al- lauh Al-Mahfuz*) surely, that is easy for Allah}.

4.2. The Crucial and Foundational Role of Germ Cell (*Nutfah*) in Fertilization and Embryonic Development

According to the dictionary of "Lisan al-Arab", the word "Al-Nutfah" means: (sperm) is the one from which the offspring come, and/or "Al-Nutfah" is the man's semen (man's fluid) [27].

The theory of creation according to Islamic doctrine derived from the Holy Qur'an is based on two foundations: the first is that the man was created from a lineage of clay (or dust), and the second foundation is "*Al-Nutfah*"/sperm, which are kept in a firm place. In addition, the term "*Nutfah* "is repeated many times in the verses of Qur'an, and in each time it gives a specific meaning varies depending on the context of the sentence. For example, it comes in the singular form to literally mean the sperm, and if it comes accompanied by the word "*Amshag*" (gamete) , then it becomes (*Nutfet Amshag*) and in this case it literally means the zygote.

The previously mentioned Qur'anic verses indicate that the "*Al-Nutfah*"/sperm (germ cell) was created as the first thing that God Almighty created to be the basic element for the creation of man. This means, most importantly, that this human existence since the first beginning of the creation is indebted to these wonderful lovely cells that God Almighty created and placed in them the secret of existence, which are the genes [28].

5. Discussion

The term embryonic development first appeared in Aristotle's book "*Generation of Animals* "and for this reason, he rightfully deserves to be considered the first developmental biologist. In the 19th century, Karl Ernst von Baer (1792- 1876) developed modern embryology through his discovery of the blastula stage of development and the notochord and became the first person to observe a human egg. In 1958, Mclaren and Biggers were the first to culture mouse embryos *in vitro* and subsequently produce a healthy live birth. In 1962, the *in vitro* culture of mouse embryos from the 1-cell stage was achieved, and the world's first human baby via *in vitro* fertilization (IVF) was born in 1978 [29].

In biological history, there are two thorny issues that have been the subject of serious debate and profound disagreement, and they are

closely related to the material and subject of the current study. The first issue is "Do females produce an equivalent to male semen, and if so, what role does female semen play in procreation?", and the second one is "Is embryonic development, substantial changes or gradual evolution? "

Concerning to the historical issue of female semen, Aristotle had argued that the female's role in procreation was wholly passive. Meaning that, the female makes no active contribution to the makeup of the offspring. While, Ibn Sina in opposition to Aristotle stated that females do produce akin to semen, which may apply to our new concept of the "ovum". [30]

Despite the importance of Ibn Sina's deduction of this crucial biological fact, he denied its generative role in procreation. This contradiction may be due to the profound influence of Aristotle's thought. After that, Ibn Sina returned to his original conviction about the inevitability of the existence of what he called "female semen", and he literally expressed this conviction in more than one place in his book, "*Kitab al-Hayawal*" (Book of Animals).

To emphasize Ibn Sina's merit and the soundness of his profound belief in the role of "female semen" in procreation, we add the following:

Ibn Sina literally says: There is nothing to prevent women from having something other than pure menstrual blood; indeed, it is very likely that women have altered blood that is closer to men's semen.

According to Ibn Sina, the reason of this altered blood is the presence of specific female organs responsible for this process, perhaps referring to the "ovaries" without explicitly mentioning them.

Then Ibn Sina adds in his decisive statement: Reproduction is a process of the male and female, and their semen together is the source of procreation; procreation cannot occur through one without the other [31].

Regarding the second issue of the precise scientific and linguistic description of the embryonic development process, is it a substantial alteration (transformation) or merely gradual changes. Ibn Sina's theory of early embryonic development was seriously and thoughtfully discussed by John Meanings in his famous reference book, "Avicenna, Great Medieval Thinkers". In this book, McGinnis, focused on, and criticized Ibn Sina's theory of embryonic development from the perspective is that it represents gradual changes rather than substantial alterations, basing his criticism on the interpretation of the word "alteration" in its Arabic origin. Our vision in this issue is summarized as follows: Firstly, word "alterations" in Arabic literally, means "transformations" (*istehala* – in Arabic), not merely changes. The process of transformation produces something entirely new second substance), impossible to revert to its original state (first substance). This description perfectly applies to the zygote, which once formed, can never return to its former form. Secondly, McGinnis reported that, "The change from semen to animal, thus, according to Avicenna, takes place through a series of discrete substantial changes, not a continuously gradual process", this statement illustrates a misinterpretation of McGinnis's conclusions, In fact, we must consciously distinguish between the substantial alterations (transformation) that occur with high precision and incredible speed in the first moments of zygote formation – as if on a divine mission, which can be called the "creative internal interaction/ or zygotic genome activation" – and the gradual changes in the embryo's size, which is the external manifestation of embryonic development as described by Ibn Sina. Thirdly, Ibn Sina in his manuscript "Treatise on Cardiac Drugs" stated that: "This divine flow that alone is capable of transforming power into action, provided that it is prepared for its perfection without apathy or miserliness". In our understanding and interpretation, the word "power" means "germ cell", while, word "action" means "fertilization". These findings of Ibn Sina is greatly applies with the data of modern embryology, which proves that, "In humans, the early embryo stage is the first eight weeks post- fertilization. At week one post fertilization the cells undergo extensive and rapid growth" [32].

For more clarification, it is worth noting that a substance can undergo two different kinds of change: accidental and substantial. An accidental change takes place when the substance is altered without disappearing or becoming a different substance. However, a substantial change occurs when the substance disappears as such or when a new substance is generated (gametes fusion → cleavage →zygote) this equation is the precise embodiment of substantial alteration [33].

The blastocyst's implantation in the uterus takes place during the second week. Although other researchers contend that" human life begins shortly after implantation of a blastocyst, on day eight after fertilization. Individuality of the blastocyst is different from that of the implanted embryo: the former can lead to twins, whereas the latter cannot. This change can be considered a substantial change since it affects the type of individuality of the primary substances involved (the blastocyst and implanted embryo), and, at this point, it should be remembered that individuality is the chief characteristic defining primary substances.

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