

The Issue of Semen with a Focus on the Unique Symphony of the Co-Evolution of Heart and Lung During Early Embryonic Development According to Ibn Sina (Kitab Al-Hayawan)

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Abstract

Regarding to natural sciences and medicine, Ibn Sina designed an applied scientific pattern based on observation and experimental analysis, perhaps his most notable contributions in this field was in Embryology, where he provided a pioneering description of the embryonic development process, as a gradual process begins from the sperm then, the clinging clot (*al-alqah*-in Arabic) and ends with the differentiation of organs, which is the main subject of the current article. The Arab-Islamic civilization was not merely a containing context for Ibn Sina but a necessary condition for his intellectual emanation. The proof is that it provided him with linguistic tools motivations for scientific research, knowledge institutions, and a translation circumference. In turn, his philosophical and medical theories played a crucial role in developing the patterns and horizons of this civilization, not only, but also in consolidating the rational methodology that characterized it throughout the ages. Sperm is the origin of creation and human existence because it carries the genetic code for this creation. Sperm composition represents an amazing uniqueness, as it is produced through a complex and precise system of creative biological processes, which in turn are subject to a system of monitoring and inspection to ensure the safety and accuracy of the genetic component it carries. Germ cells are the source of heritable genetic variation, and they produce the totipotent zygote from which embryogenesis commences. Embryogenesis is essentially a highly coded and coordinated series of genetic processes. Genes expressed during spermatogenesis encode proteins both for general activities and for processes specific to germ cells. The first serious scientific attempt to describe human sperm was made by van Leeuwenhoek in 1677. Following this in 1678 Huygens published a letter in *Journal des Scavans* with first mention of spermatozoa, based on van Leeuwenhoek's observations. Later on, Enrico Sertoli described the columnar cells running from the basement membrane to the lumen of the seminiferous tubules including unique branches of the cell's cytoplasm that supported germ cell development. Arnold Berthold (1803-1861) was the first to provide conclusive evidence that the testes have an endocrine role, and he concluded that the regulation of male characteristics is carried out through factors transmitted via the blood. Sperm metabolism is recognized as flexible, responding to environmental conditions and energetic demands during ejaculation, the journey along the female tract, and until fertilization.

This article aims to elucidate the unique philosophical and scientific notions that accompanied Ibn Sina's significant contribution of the study and analysis of early embryonic development. It focuses on two key aspects: firstly, Ibn Sina's insightful awareness of the presence of the genetic component inside the head of the sperm, and was the first to describe the sperm as a "latent power". Secondly, his vision and discovery of the symphony of integrative co-evolution the heart and the lung as if he was witnessing it firsthand in the distant depth of the early embryonic development.

Keywords: Ibn Sina, Early Embryonic Development, Sperm, Co-Evolution of Heart and Lung, *Kitab Al, Hayawan*

1. Introduction

The Arab-Islamic civilization was not merely a containing context for Ibn Sina but a necessary condition for his intellectual emergence. The proof is that it provided him with linguistic tools motivations for scientific research, Knowledge institutions, and a translation environment. In turn, his philosophical and medical contributions played a crucial role in developing the patterns and horizons within this civilization, not only but also in consolidating the rational methodology that characterized it [1].

Regarding to natural sciences and medicine, Ibn Sina designed an applied scientific pattern based on observation and experimental analysis, perhaps his most notable contributions in this field was in Embryology, where he provided a pioneering description of the embryonic development process, as a gradual process begins from the sperm then, the clinging clot (*al-alaqah*-in Arabic), and ends with the differentiation of organs, which is the subject of the current article.

Ibn Sina challenged Aristotle's theory, which is based on the hypothesis that the origin of creation (procreation) is attributed only to the father, and in the face of this theory, Ibn Sina emphasized that procreation takes place through both male and female semen. Moreover, he was able to identify the heart as the first organ to form in the fetus, In addition, he was the first to explain the vital role of the placenta in the exchange of nutrients necessary for growth, and this understanding was a scientific precedent confirmed by subsequent anatomical discoveries [2,3].

Throughout history, no word or notion has garnered as much discussion, attention, and confusion as the word "sperm". However, the association of the term with the reality of existence and creation added to it an aura of sanctity and crucial importance. Accordingly, scientists, thinkers, and philosophers have strived to search and unravel the mystery of this term as well as explore the mechanism that governs the operation and development of this small creative cell. The aim of the current article is to highlight the hidden scientific aspects in Ibn Sina's thought on this issue and to demonstrate the essence of this thought and diligence, as Ibn Sina was the first to coin and realize the concept of "latent power" to describe the sperm as a creative genetic code [4].

1.1. The Intertwined Rooting of Cultural History of Mythological, Popular Belief, and Religions of the Sperm

In some cultures, semen is attributed with special properties of masculinity. For instance, some African people believe that young

boys must fellate their elders and ingest their sperm to achieve proper sexual maturation [5].

In ancient Egyptian culture, semen was regarded as a sacred, powerful, and divine substance, intrinsically linked to creation, fertility, and the life-giving properties of the Nile. It was viewed not just as a biological fluid for reproduction, but as a potent force that originated from the gods and was crucial for maintaining cosmic order. Furthermore, the fertility and divine power, linked to gods like Min and Sobek, and seen as the force behind Nile floods and regeneration, with texts describing divine infusion into bones and surprising depictions of sperm-like structures in art, blending empirical observation with spiritual belief in a holistic understanding of reproduction [6].

In Greece philosophy, Aristotle remarked on the importance of semen, by emphasizing that the semen is the residue derived from nourishment that is of blood, which has been highly concocted to the optimum temperature and substance. This can only be emitted by the male as only the male, by nature of his very being, has the requisite heat to concoct blood into semen [7].

In other words, sperms are the excretion of our food, or to be precise, as the most perfect component of our food [8].

Aristotle summarized the relationship between sexual activity and physical growth of the body in a clear statement, asserting that engaging in sexual activity at a young age would inevitably affect the rate of physical growth because the nutrients that were supposed to nourish the body would be diverted to the production of seminal fluid. Therefore, Aristotle preferred that sexual activity begins only after the body has reached its normal growth rate [9]. Additionally, Pythagoras expressed his belief that semen is a drop of the brain. Aristotle influenced by this theory stated that seed (germ cell) comes from liquid in the region of the eyes [10,11].

Indian philosophy believes that the theory of creation begins when the Supreme Self transmute itself to become the creature through immense and arduous effort (Srama). This transformation is only completed through heat (Tapas), which is the decisive element in the entire creative process. This understanding aligns with what is stated in Sanskrit literature, which interprets "Tapes" as a reference to the sexual heat or warmth that incubates the birth of life. Perhaps the juxtaposition of the words Kama (desire) and Tapas (heat) explains the nature of the feelings and energy that leads to intercourse [12,13].

“*Shukra*” is the accepted term to describe both male semen (sperm) and female semen (egg) in the philosophy of Ayurveda. People with healthy “*Shukra*” appear stronger and confident, with eyes and skin that seem lustrous. Ayurveda philosophy is tolerant of celibacy or monasticism and does not strictly consider morality as a part of sexual life; they believe that the health and strength of male organ (*Shukra*) and its religious duty (*Dhrama*) are the primary criteria for sexual activity [14].

The ancient Sumerians believed that semen was "a divine substance, endowed on humanity by Enki", the god of water. The semen of a god was believed to have magical generative powers. In addition, they also believed that rain was the semen of the sky-god An, which fell from the heavens to inseminate his consort, the earth-goddess Ki, causing her to give birth to all the plants of the earth [15,16].

In Islamic doctrine and philosophy, the notion of sperm holds immense importance. This importance and significance is underscored by the numerous verses in the Holy Quran that affirm sperm as the biological and spiritual base of the creation. Then, these are some Qura'nic verses that confirm this concept: 1-Surah Al-Mu'minun (The Believers) No.23/18, verses 13 and 14:2-Surah Al-Hajj, (The Pilgrimage) No.22/17, verse, 5: 3-Surah Fatir, (The originator of Creation or The Angels) No.35/22, verse 11 [17].

From these verses and other related ones, the accuracy of the divine description of the sperm as the seed of fertilization and the essence of divine creation becomes clear to us.

The process of embryonic development is guiding us to discover the first genetic notion contained in a Holy Quran. Based on this noble Qur'anic narrative, Ibn Sina endeavored to study embryonic development and the crucial role of the sperm in this creative process. Ibn Sina was able to present a remarkable text in explaining and interpreting the stages of this embryonic development, considering it as an indicative and suggestive embodiment of the theory of divine creation [18].

1.2 The Intertwined Scientific, Biological, and Creative Role of Sperm

During ejaculation, sperm passes through the ejaculatory ducts where it mixes with fluids secreted from the seminal vesicles, prostate gland, and the bulbourethral glands to form the semen. The seminal vesicles produce viscous fluid rich in fructose that constitute about 70% of human semen. The prostatic secretion contains proteolysis enzymes, citric acid, acid phosphatase and lipids. As for the bulbourethral gland is responsible for secreting of a clear fluid to lubricate the urethra [19,20].

Sperm formation is one of the most complex and precisely regulated biological processes because it involves a few checkpoints to ensure the production of a high-quality and accurate DNA product. Therefore, it is not without reason that sperm cells are considered uniquely gifted. Balancing quantity and quality in sperm production

is thus a delicate process, subject to specific cellular and molecular control mechanisms, and sensitive to environmental conditions, that can impact fertility and offspring health [21].

The life cycle of a sperm divided into four basic stages: 1- spermatogenesis—the process by which diploid spermatogonia undergo meiosis and morphological alterations to produce sperm; 2- post testicular maturation and storage—the moment after spermatogenesis but before ejaculation, in which sperm interact with extracellular proteins, lipids and microRNAs, among other molecules; 3- capacitation—the moment after ejaculation in which sperm effectively acquire the capacity to fertilize oocyte; and 4- fertilization—the process by which the spermatozoon penetrates the oocyte's outer protective layers and transfers its genomic material to the oolemma, the initial step in the formation of a zygote [22-24].

Sertoli cells, which nurture and support developing spermatocytes, secrete a fluid into seminiferous tubules that helps transport sperm to the genital ducts. The seminal plasma provides a nutritive and protective medium for the spermatozoa during their journey through the female reproductive tract. Basic amines such as putrescine, spermine, spermidine and cadaverine are responsible for the smell and flavor of semen. These alkaline bases counteract and buffer the acidic environment of the vaginal canal, and protect DNA inside the sperm from acidic denaturation.

Sperm metabolism is a flexible, responding to environmental conditions and energetic demands during ejaculation, the journey along the female tract, and until fertilization.

Various studies suggest that sperm metabolic functions are relevant beyond fertilization and may influence zygote and embryo development, impacting paternal-derived effects on offspring development and health. Recently, sperm metabolic function and homeostasis has gained serious and increasing attention in scientific research dedicated not only to male fertility but also to study fertility and reproduction in general [25-28].

Garbers and his colleagues have worked with livestock species, thus leading to an understanding of sperm metabolism in animals beyond the traditional laboratory rodents. These studies highlighted the role of phosphodiesterase (modulated by the action of caffeine) and nucleotide-mediated effects (cAMP and cGMP) in bull epididymal and ejaculated sperm motility and metabolism [29-31]. Studies in boar sperm highlighted further the role of cAMP in the regulation of sperm motility [32]. Based on these results, Garbers and colleagues characterized bull spermatozoa cAMP-dependent protein kinases. During these years, Garbers and colleagues also inquired about the effect of different energetic substrates on sperm motility, phosphodiesterase action, and other related metabolic markers. Thus, working with different species, they contributed to elucidate shared metabolic pathways and identify species-specific divergence.

The sequential historical development of sperm concept and semen technologies can be summarized as follows:

- 460-370 BC: Democritus suggests that females originate from the left testis and males from the right.
- 460-370 BC: Hippocrates argues that generation takes place through the joint action of two kinds of semen, one from the male ejaculate, the other from the female's menstrual blood.
- 350 BC: Aristotle publishes *De generatione animalium*. He believed that only the male's semen or 'seed' contributed to the 'form' of the foetus which was imprinted onto the 'matter' provided by the menstrual blood of the female.
- 129-200 BC: Galen supports the assertion of Hippocrates that the seeds of both the male and female contribute to generation.
- 1651- Harvey publishes *Exercitationes de generatione animalium* with the famous frontispiece illustrating the Greek god, Zeus, liberating all creation from an egg bearing the inscription 'ex ovo omnia'
- 1668- De Graaf describes the structure of the testis.
- 1677- van Leeuwenhoek reports the first description of (human) sperm and illustrates sperm of a rabbit and dog to the Royal Society. Eventually published in 1679.
- 1678- Huygens publishes letter in *Journal des Scavans* with first mention of spermatozoa, based on van Leeuwenhoek's observations.
- 1694- Hartsoeker publishes speculative drawing of homunculus in sperm [33,34].

Although the testicles control over male characteristics, but they provided no evidence regarding the mechanisms involved. It was not reported until the seventeenth century that a detailed account of testicular and penile anatomy was presented by de Graaf in his treatise on the male reproductive organs. In an experiment in mice De Graaf reported that the testicle is a collection of minute vessels or tubules [35].

Arnold Berthold (1803-1861) was the first to provide conclusive evidence that the testes have an endocrine role, and he concluded that the regulation of male characteristics is carried out through factors transmitted via the blood.

In 1840, von K llicker discovered that spermatozoa develop from cells located in the seminiferous tubules. This was followed by the description of the microscopic characteristics of the interstitial cells by German zoologist Franz Leydig's which are a meshwork of loose connective tissue filling the spaces between the seminiferous tubules and blood vessels [36,37].

Later on, Enrico Sertoli described the columnar cells running from the basement membrane to the lumen of the seminiferous tubules including unique branches of the cell's cytoplasm that supported germ cell development [38].

2. Material and Methods

- Appendix 1: Original text of Ibn Sina in Arabic.
- Figure 1 (A B C): In vivo co-development of heart and endoderm with emphasis on the co-emergence with the lung.

- Figure 2 C: Illustration credit: Ben Smith, hiPSC indicates human – induced pluripotent stem cell.
- Translation of Ibn Sina's text from Arabic into English.

Translation of Ibn Sina's text with preliminary explanation and clarification in brackets.

Title: On how animals reproduce from sperm and eggs, and the differences between animals in this regard and how the sperm (and its equivalent) are accepted the psychological faculties that accompany it. *

Let's examine and test the state of the semen, and whether it contains a part of soul, I mean the power [i.e., **the germ cell/sperm/Nutfah**] **, or whether it is devoid of sperm (**Azoospermia**).

Since the semen moves to form the embryo not because of some external factors, but due to its nature, which is guided by God Almighty's permission, it contains the principle of the nourishing soul (**blood**). The organs are not formed from it all at once (**meaning that all organs are not formed from this soul at once**) the experience indicates that the heart is the first to develop. It is inevitable that someone who has no heart may have another organ instead of the heart. The heart is also the last organ to die and when the lungs are formed, breathing begins.

(This text carries dialectic, philosophical and medical terms, indicating that since the heart forms first, it is responsible for supplying the embryo with blood, which represents nourishment and oxygen. Therefore, the cessation or death of the heart means the end of life; hence the heart is the last organ to die. Furthermore, the text is also replete with eloquence, sophistication, poetry and the beauty of the Arabic language, where the words correspond to the demands of the situation and are concise in meaning, both linguistically and rhetorically. This means expressing the contrast between words in a brief phrase: the first to be born and the last to die).

What is said that the lungs do not appear in the embryo, while the heart is apparent, does not mean that they were present but hidden due to their small size. The lungs of embryo are larger than the heart. It does not appear along with the heart, because they form later. If the concealment was due to smallness, then what is smaller would be more concealed, and the heart would be more deserving of concealment than the lungs. However, the act of the father implanting into the mother's implant occurs only by way of encounter of the mover (**sperm**) and the moved (**egg**), **(This refers to the fertilization process as a precursor to zygote formation)**, As for the agent of blood (**meaning the source of blood flow**) from which the semen is generated, and from which the child is born, it is the liver or the heart (**expressing the ancient primary dispute in the Greek philosophy about the initial source of blood, whether it is the heart or the liver**).

As for its composition, semen is formed in the seminal vesicles **(that is the blood transformed (istehal- in Arabic) into semen**

and is created in seminal vessels), and this sperm stimulates something else, that is, the woman's semen/*Nuttah* (**woman's ovum**), resulting in the formation of the first principle (**the zygote/first perfection**). From this zygote emanates a power (**faculty/functional genes**) that undertakes the task of forming all organs in order, and this formed sperm/fertilized ovum (**zygote/Nutfet amshag in Arabic**) has become a self (alive) by the strength of the male's influence on it.

The soul is like being born (generated) from the male sperm, and the body from the female semen "ovum".

When this (**embryo**) develops the ability to breath (becomes alive), then the soul moves within it towards the completion of the organs. This soul is then a nourishing soul (blood), or it has no other function, even if it has the power to do otherwise (**this is a definitive, emphatic formulation of Ibn Sina, meaning that the soul/blood is only available to nourish the embryo and supply it with oxygen, as this is its inevitable, predestined function, and nothing else**).

And if the sperm prepares the nourishing power (**faculty**) to receive/accept actions intended for the soul (**which is the immaterial faculties, such as: psychological/moral/intellectual/mental faculties, distinguishing it from the physical faculties "body organs"**), then it must also possess a power (**faculty**) with specific characteristics corresponding to the immaterial nature of the soul, and this notion may point to the initial preliminary concept of genetic compatibility between the physical faculties "body organs" and immaterial faculties "soul"). The spiritual aspects of the pronunciation (**human being**) are of one nature, because the spiritual/rational and vocal organs are formed together in these beings. Nor do the nourishing spirit and its organs apply. (**Meaning that: since the spiritual aspects in rational beings are of one nature with one genetic component, this means that the spiritual and rational organs share together a unique genetic structure "subtle/fine mixtures) that enables them to fulfill their creative function, and perhaps these intended genetic structures - in the language of our time - are: chromosomes/genes of intelligence, psychology, thought and logic. And then, the previous interpretation of rational beings does not apply to the nourishing soul and its physical organs**). Furthermore, the animal's organs are not endowed with spiritual, but rather with the ability to accept food (nourishment). It is possible that the nourishing soul inherited from the father remains until the *mizaj* (**genotype**) undergoes a transformation, at which point the specific nourishing soul joins it.

(This is a very early, primal genetic text par excellence, because the Arabic term "mizaj/ and or mazaj" correspond to the English term "genotype", and the text literally refers to the meaning of genetic matching between the soul and body, may be at the moment of "the first division of the zygote cell into cleavage)."

It seems that the benefit from the father does not reach the ability

to complete the planning to the end (**the sperm alone cannot accomplish the task of fertilization lonely**), but rather it fulfills the planning of what needs a strong origin (**and to achieve that it needs a second equivalent origin, which is the egg**).

As if the father's semen contributed to the fertilization process has changed from what it should be, then, it is not from the type of absolute nutrient that was in the father and that is in the son.

(meaning simply that after fertilization, the male sperm material has radically changed/alterd (istehalat in Arabic) by merging with the egg; with this change, the concept of the absolute sovereignty of a man's sperm alone has become incorrect, or more precisely inconclusive, as was believed in ancient Greek thought, especially by Aristotle).

Be that as it may, if the heart and brain are formed within the body, the rational soul becomes attached to them, and the spiritual soul emanates from them. The rational soul, however, is distinct and immaterial, and it is perfected by something external that benefits the mind/intellect. As for the other faculties, they are perfected through the body and physical matters.

(When the heart and brain have developed in the zygote, the rational soul connects with the brain and together they form a lifelong integrated unit, and the mind/intellect becomes the essence of this soul according to Ibn Sina's philosophy).

In the semen there is an "essence" that is the first essence that accepts it, which is the soul (**this essence can be considered as the "germ cell/sperm" with its genes**), which is the reason for collecting the semen's parts, and it is the agent of the semen and its maturation, and it is separate in itself (**meaning, it is specific and unique essence, because it is the secret of existence, creation, and formation of all living being**), so if it separated from the semen it becomes decays and decomposed (**that is, the semen has no value without the germ cell, because it is the ruling and controlling essence, and it is the secret of creation from the perspective of the theory of divine creation**).

This soul/essence is a divine body (**perhaps we disagree with Ibn Sina that it is a body; more precisely, it is a divine code**), its relation to semen and organs is like the relation of the intellect to the psychic faculties (**this true and inevitable equation signifies the precision of Ibn Sina's logic, his profound awareness, and his unique deduction. Here, he aptly points to genetic equilibrium, since the term "germ cell" is fundamentally and literally a genetic term**).

The mind is the best non-corporeal essence, and the soul (blood) is the best corporeal essence. This essence (**soul/blood**) does not leave the semen as long as it is correctly and accurately intact in the womb, but rather it transforms the semen into its essence (**i.e., germ cell**), so it dissolves, becomes refined, and becomes spirit (**the germ cell with all its sacred genes, which is the first substance/essence of creation, and Ibn Sina's terminology of**

“dissolves” and “ becomes spirit, may indicate that this essence is a code and nothing else, and the code in this context is none other than the gene). Then the formed zygote (*Nutfat amshag*) is filled with spiritual wind, and this spirit becomes a penetrating spirit that forms the organs by its faculties (genes) and perfection is achieved for these organs [39].

**** (The text within brackets represents the author’s attempt to adapt and interpret Ibn Sina’s text in its original language “Arabic”)**

3. Interpretation and Discussion

In the previous lines, we have provided a translation of Ibn Sina’s text accompanied by some implicit and deductive explanations as an attempt to present the text in the closest and clearest understanding, and now we provide a deeper explanation and interpretation of some of the main axes:

3.1. Ibn Sina’s Insight in Understanding the Genetic Essence of the Sperm

Let’s examine and test the state of the semen, and whether it contains a part of soul, I mean the power (i.e., the germ cell/sperm/Nutfah in Arabic), or whether it is devoid of sperm (Azoospermia).

This statement represents the systematic and institutional understanding of Ibn Sina’s style when he always writes on academic issues. He is discussing the absolute necessity of examining, studying and analyzing the semen. The cause is to ascertain the presence of sperm which represents the creative power of this seminal fluid. Or does this fluid not contain any sperm at all (which is called in the language of our time as: Azoospermia).

The first serious scientific attempt to describe human sperm was made by van Leeuwenhoek in 1677. Following this in 1678 Huygens published a letter in *Journal des Scavans* with first mention of spermatozoa, based on van Leeuwenhoek’s observations [40].

The question is how Ibn Sina was able to draw inspiration from and grasp these notions more than half a century before the mid-17th century, and how he expressed them in the most precise and beautiful possible terms, with definitive meaning, as if he saw them with his own eyes, and even described them in their sound scientific form as the “latent power” [4].

The term of “latent power” first appeared in Ibn Sina’s manuscript “Treatise on Cardiac Drugs” and came in a complete philosophical, biological, genetic and divine context, as follows: “This divine flow alone is capable of transforming power “sperm/germ cell” into action (fertilization/zygote/cell division), provided that it is prepared for its perfection without apathy or miserliness [41]. (In the sense of: the process of extensive and rapid growth/multiple rapid division must be carried out in an absolutely perfect manner because, according to Ibn Sina, the zygote is the first perfection). To reinforce and confirm what Ibn Sina had previously deduced, scientists recently discovered that in humans, the embryo stage is the first eight weeks post- fertilization. At week one post

fertilization, the cells undergo extensive and rapid growth [42]. Furthermore, the idea put forward and formulated by Ibn Sina in this distant era- that seminal fluid may contain sperm, thus becoming potent and creative due to the sperm’s power or it may not contain it, thus becoming useless- this understanding of Ibn Sina has found its full application in modern reproduction and Andrology sciences. From this perspective, we can review some terms that confirm the validity and greatness of Ibn Sina’s thought. Azoospermia is defined as the complete absence of sperm in the ejaculate, occurring in 8% of infertile men, and can result from obstruction of the extra testicular ductal system or defects in spermatogenesis. Aspermia is defined as the absence of fluid in the semen, contrasting with azoospermia, which specifically refers to the absence of sperm within the semen. Oligozoospermia, also known as oligospermia or low sperm count, is a male fertility condition where semen contains fewer sperm than normal, typically below 15 million per milliliter. Asthenozoospermia is a male fertility issue characterized by reduced sperm motility. Resulting in sperm doesn’t swim effectively, retardation of their ability to reach and fertilize an egg, and making natural conception difficult. Cryptozoospermia is a male infertility condition with an extremely low sperm count, where sperm aren’t seen in routine semen analysis but are detected after the sample is centrifuged and examined closely, distinguishing it from azoospermia (zero sperm) [43].

3.2. The Unique Co-Evolution of the Heart and Lung During Embryonic Development

“The experience indicates that the heart is the first to develop. It is inevitable that who has no heart may have another organ instead of the heart. The heart is also the last organ to die. And when the lungs are formed, breathing begins”.

This paragraph encompasses more than one discipline; it belongs mainly to embryology, as well as anatomy, philosophy, and physiology. Ibn Sina’s observation regarding the connection between heart and lungs during early embryonic development may be the first conscious and insightful observation in the history of human medicine.

Then, the first issue is why the heart and lung were the focus of Ibn Sina’s attention in his initial understanding of the embryonic development process? In fact, the answer to this question regarding the heart extends from Aristotle to Ibn Sina; in that Aristotle was the first to give the heart its supremacy and utmost importance as the first organ to form in the zygote, Ibn Sina, however, went beyond Aristotle and corrected his concept, asserting that blood, not the heart, is the first organ that is created in the early stage of embryonic development, and the heart comes immediately after, meaning that the heart is the gift of blood. The proof is blood cell development begins as early as the seventh day of embryonic life [44]. In this regard, and for further clarification, Ibn Sina proceeded from an early conviction that no one had realized before, namely, that the heart and blood represent an “eternal integrative unit”, although he had acknowledged that the heart is the first organ formed influenced by Aristotle, but in fact he was concerned with

this eternal integrative unit, which Embryology has proved in its modern edition that blood cells are the first cells formed, and then the heart comes after it. It is these very cells that play the main role in its formation, and this explains the fact that together they are a complete fusion unit, descriptions of which cannot be imagined one without the other.

Another confirmatory proof is through early development; the primitive vasculature expands, remodels, and specializes in achieving the critical metabolic demands of the tissue it supplies. As a result of this remodeling process, the endothelial cells lining the cardiovascular system subspecialize into atrial, venous, lymphatic, and haemogenic fates via a complex network of intersecting molecular pathways [45].

Then, the blood island integrates to form vascular channels and a plexus network throughout the yolk sac, which conducts oscillatory plasma flow driven by the developing heart tubule [46]. Then, Ibn Sina gave the heart its crucial importance as the repository of the soul “blood”. This integrative unit between the heart and blood continues and is reinforced after the oxygen molecules from the lungs joins them, so that they all become the enduring process of life going on for a while. This again points to the secret behind Ibn Sina's early and inspiring interest in the need to understand the relationship between the heart and the lungs.

With regard to the embryonic development of the lungs, it can be summarized as follows:

- **Embryonic Stage** (Weeks 4–7): Development starts with the appearance of a lung bud (respiratory diverticulum) from the primitive foregut. By the end of this stage, the trachea, the two primary bronchial buds, and the precursors to the lung lobes and segments are formed.
- **Pseudo glandular Stage** (Weeks 5–17): The bronchial buds undergo extensive branching to form the entire conducting airway system, down to the terminal bronchioles. The lungs resemble an exocrine gland during this phase, and no gas exchange is possible.
- **Canalicular Stage** (Weeks 16–26): The lung tissue becomes more vascularized as capillaries form a dense network around the developing air spaces (respiratory bronchioles and alveolar ducts). Type I and type II pneumocytes begin to differentiate, and small amounts of surfactant are produced, making survival for premature babies possible with intensive care towards the end of this stage (around 24-26 weeks).
- **Saccular Stage** (Weeks 24–38): Terminal sacs (primitive alveoli) form and expand, significantly increasing the surface area for gas exchange. Surfactant production increases substantially, and adequate amounts for breathing are usually present by about 32-36 weeks.
- **Alveolar Stage** (Week 36 – Childhood): Mature alveoli, the primary site of gas exchange, begin to form just before birth and continue to multiply rapidly after birth through secondary septation. The number of alveoli reaches the adult count (around 300 million) by approximately 8 years of age [47-49].

- Development of the lower respiratory tract begins on day 22 and continues to form the trachea, lungs, bronchi, and alveoli. The process is divided into five stages: embryonic, pseudo glandular, canalicular, saccular, and alveolar stage. Although the process begins early in fetal development, complete maturation does not take place until the child is approximately 8 years of age. This developmental delay is vital in premature babies where their survival is intricately linked to which developmental stage their respiratory tract has reached at the time of birth.

The current review of the stages of development of the lungs proves two paramount facts:

Firstly, the development of the lungs is a prime example of how different organs mature at varying rates, with the lungs being one of the last systems to become fully functional.

Secondly, this irrefutable fact fully applies and confirms the correctness of Ibn Sina's vision when he pointed out in his text that the formation of organs in the zygote does not take place all together at the same time. He stated:” It (lung) does not appear along with the heart, because it is formed later”.

The second issue concerns the symphony of three-dimensional, -philosophical, biological, and anatomical dialectical relationship-between the combined embryonic co-evolution of both the heart and lung.

In this respect, the following explanation based on the data from modern human embryology may fully confirm what Ibn Sina concluded by his unique acumen.

It goes without saying that human embryogenesis is a sophisticated process that demands sensitive coordination between organs that originate from different germ layers. Within the chest cavity, the heart and lung derived from the mesoderm-and endoderm- layers, respectively have extensive mutual interaction that are essential for their proper morphogenesis [50-53].

Much research on embryonic organogenesis has discovered main mechanisms regarding how tissue morphogenesis is regulated by interactions among cells within each individual organ, including the mesoderm-derived heart and the endoderm-derived lung or intestine. However, accumulating proofs suggest how important the inter-organ and cross-lineage communications occur between the heart and endoderm derives organs in the individual co-developmental programs (Figure 1) [54,55].

The differential growth of the cardiac mesoderm and adjacent endoderm is motivated by their diagonal folding and elongation through a process called convergent extension during the folding of endoderm to form the foregut tube along the body's midline [56-57]. The bilateral heart primordia also fold toward the midline and fuses to give rise to the heart tube located ventrally to the newly emerged foregut (Figure 1A and 1B) [53].

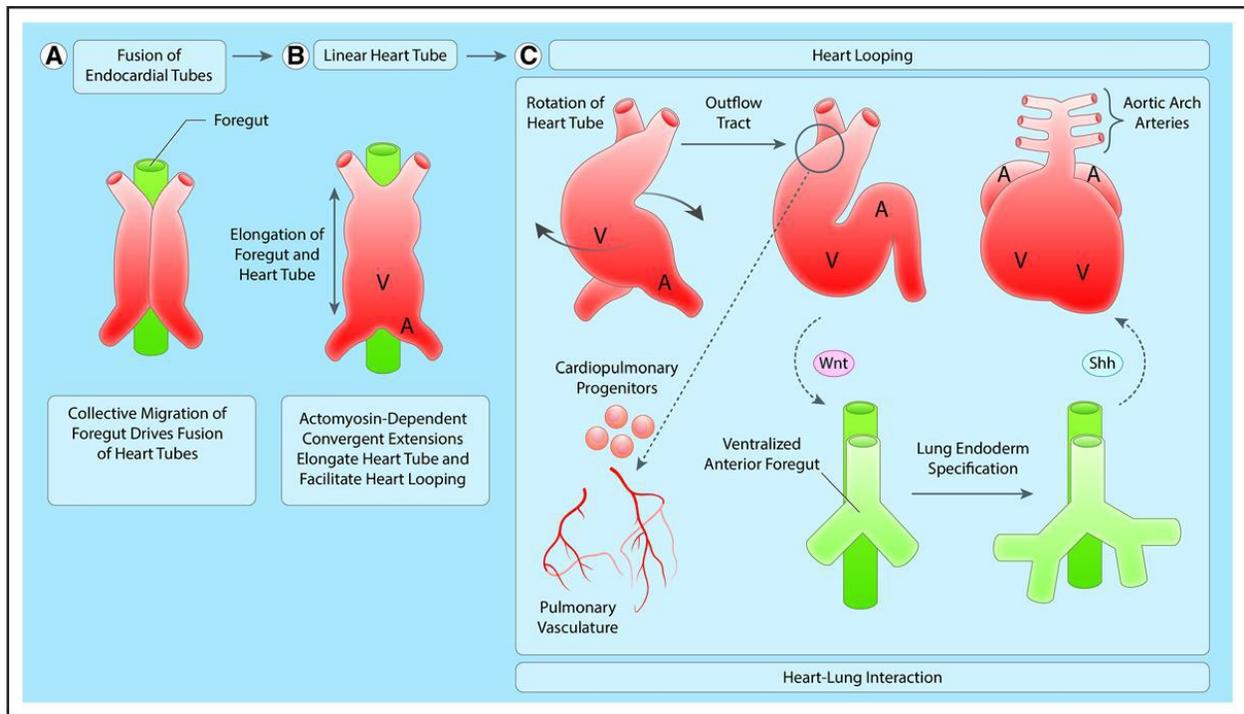


Figure 1: (A, B, C): In vivo co-development of heart and endoderm with an emphasis on the co-emergence with the lung. Illustration credit: Ben Smith (Ng et al., 2023)

The fundamental role of the adjacent endoderm in the migration of cardiac mesoderm is well demonstrated by the removal of foregut endoderm resulting in cardiac bifida [58, 59].

The cardiac mesoderm has a regulatory role in the maturation of the co-developing pulmonary epithelium (Figure 2C) [60].

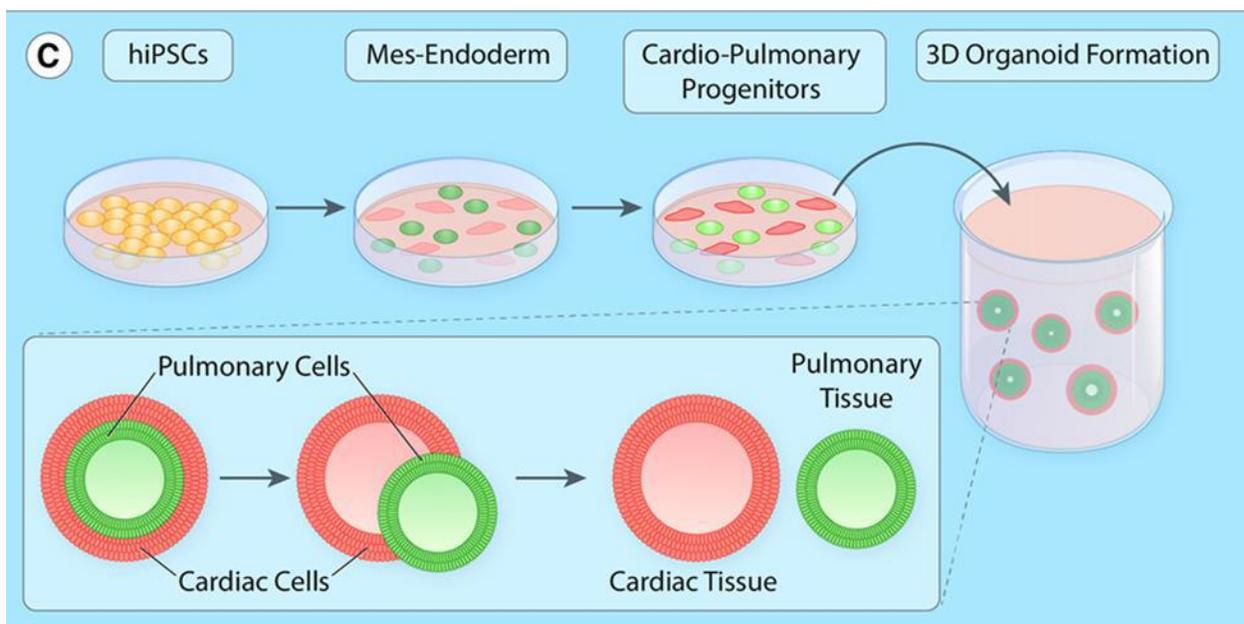


Figure 2 C: Illustration credit: Ben Smith. hiPSC indicates human-induced pluripotent stem cell (Ng et al., 2023)

The simultaneous differentiation of human-induced pluripotent stem cells into lung progenitors (NKX2.1+) and cardiac progenitors (NKX2.5+) is modulated by Wingless-related integration site (WNT) and Nodal signals in the same culture. At first, the concentration of CHIR99021 (WNT agonist) was titrated to facilitate a balanced induction of mesoderm and endoderm [61,62]. Then the dual inhibition of both WNT and nodal signaling was inhibited to direct the specification of germ layer progenitors towards cardiac mesoderm and anterior foregut endoderm fate. Similar reports were obtained by Drakhlis *et al.*, 2021, and Silva *et al.*, 2021 [63, 64]. Where WNT signaling was activated and then inhibited to enable effective induction of both cardiac and endodermal derivatives. This close spatial proximity of the co-developing cardiac and endodermal lineages within the embryonic body patterning assures that both of their fates are influenced by the exposure to a similar set of paracrine factors [63].

At day 15 of differentiation, the co-induced cardiac and pulmonary progenitors were aggregated in an extra cellular matrix (ECM)-free suspension culture to induce the formation of three dimensions dual-lineage organoids and tissue maturation. Initially, an outer layer of cardiac tissue formed to encapsulate the pulmonary component centrally located. The presence of the cardiac tissue accelerated the maturation of the pulmonary progenitors into Surfactant Protein C (SFTPC+) alveolar type 2 cells within as short as 3 days in 3D suspension culture. This finding echoes the cardiac-assisted pulmonary specification observed in mouse embryogenesis has a great sound in human gastrulation [53].

3.3 The Theory of Transformation of Blood into Semen

As for its composition, semen is formed in the seminal vesicles (that is the blood transformed (istehal) into semen and is created in seminal vessels), To confirm the accuracy and correctness of this early idea of Ibn Sina, it should be noted that Vonkollicker, in 1840, discovered that spermatozoa develop from cells located in the seminiferous tubules [36,37]. And this sperm stimulates something else, that is, the woman's semen/Nuttah (woman's ovum), resulting in the formation of the first principle (the zygote/first perfection). From this zygote emanates a power (faculty/functional genes) that undertakes the task of forming all organs in order, and this formed sperm/fertilized ovum (zygote/Nutfet amshag in Arabic) has become a self (alive) by the strength of the male's influence on it.

The seminal vesicle (SVs) is defined as a pair of tube-like glands located behind the bladder in males, which produce approximately 70% of the content of semen. The seminal vesicles are a pair of male accessory reproductive glands, located posteroinferior to the urinary bladder. The SVs actively produce secretions that compose the majority of the fluid element of semen. Since SV secretions serve to protect sperm [65].

Ibn Sina's theory regarding the formation of semen from blood appears to be influenced by Aristotle's contributions on this matter, who said that "the semen is the residue derived from nourishment that is of blood, which has been highly concocted to the optimum

temperature and substance. This can only be emitted by the male as only the male, by nature of his very being, has the requisite heat to concoct blood into semen" [3].

Concerning to the zygote's power of Ibn Sina is, in our view, nothing but the integrative unity between the soul/blood and functional genes "sacred pairing theory" that build the organs of the embryo [66].

3.4 Duality of Heart and Brain

If the heart and brain are formed within the body, the rational soul becomes attached to them, and the spiritual soul emanates from them. The rational soul, however, is distinct and immaterial, and it is perfected by something external that benefits the mind/intellect. As for the other faculties, they are perfected through the body and physical matters.

In the 3rd week of embryonic development, the nervous system begins to form, with a primitive streak appearing as a groove in the epiblast layer of the bilaminar disk. Cells within the epiblast migrate downward through the primitive streak, resulting in the rise of three germinal layers, which are, endoderm, mesoderm, and Ectoderm. The nervous system is derived from the ectoderm, which is the outermost layer of the embryonic disc [67]. 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 [68]. 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 [69].

Then, it can be concluded that there is a significant convergence in the developmental stages of the heart and brain, but in a precise and controlled balance, which confirms Ibn Sina's initial vision and understanding of the stages of embryonic development. But this convergence in the case of the heart and brain does not amount to the case of the co-evolution of the heart and lungs.

This context is a faithful translation of the dualities of soul and body, brain and intellect, and/or any physical/immaterial duality, and the pattern of the eternal complementary relationship between them, and this is one of the key pillars in Ibn Sina's philosophy. The Human intellect consists of two parts: "theoretical intellect", its function is to deduce and reproduce thought, and knowledge. Second intellect is the "practical one", which directly works to apply this thought and knowledge in reality, the physical and/or spiritual code link between the two intellects still needs further in-depth research. Regarding to this physic-spiritual link, Immanuel Kant suggested that the theoretical (pure) reason can contain within itself a "practical principle" that is capable of determining the will by which practical laws (the activity of practical reason) are realized. Otherwise (meaning the absence of this practical

principle), all practical laws become mere axioms [70].

In fact, the dialectic relationship between the soul and mind is one of the greatest signs of Ibn Sina's genius. The mind for Ibn Sina did not disappear from the soul, but rather it is hidden in its core, while in Descartes' philosophy the soul was never mentioned in its necessity of being linked to the mind, and the evidence is: according to Ibn Sina the soul is the capital notion in his philosophy, and the body is nothing but a means to achieve the perfection and brilliance of the soul. Therefore, the term "soul" for Ibn Sina never comes separately from the concepts of blood and mind (intellect), "Aql" in Arabic, that because the mind is the active essence of the soul, and it acts as the complementary part of the divine code of the soul.

So, they together represent the eternal union of the divine creation theory.

In fact, Ibn Sina, before everyone else, had spoken about this "practical principle" and called it the "active intellect", which is pronounced in Arabic as (الأعقل الفاعل) and it is active because it simply has the awareness and will.

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Appendix 1

Translation of Ibn Sina's text from Arabic into English

On how animals reproduce from sperm and eggs, and the differences between animals in this regard and how the sperm (and its equivalent) are accepted the psychological faculties that accompany it.

Let's examine and test the state of the semen, and whether it contains a part of soul, I mean the power, or whether it is devoid of sperm. Since the semen moves to form the embryo not because of some external factors, but due to its nature, which is guided by God Almighty's permission, it contains the principle of the nourishing soul. The organs are not formed from it all at once. The experience indicates that the heart is the first to develop.

It is inevitable that who has no heart may have another organ instead of the heart. The heart is also the last organ to die. And when the lungs are formed, breathing begins.

What is said that the lungs do not appear in the embryo, while the heart is apparent, does not mean that they were present but hidden due to their small size. The lungs of embryo are larger than the heart. It does not appear along with the heart, because they are formed later.

If the concealment was due to smallness, then what is smaller would be more concealed, and the heart would be more deserving of concealment than the lungs.

However, the act of the father implanting into the mother's implant occurs only by way of natural actions and formation, most of which are by way of encounter of the mover and the moved, As for the agent of blood from which the semen is generated, and from which the child is born, it is the liver or the heart.

As for its composition, semen is formed in the seminal vesicles, and this sperm stimulates something else, that is, the woman's semen/*Nuttah*, resulting in the formation of the first principle. From this zygote emanates a power that undertakes the task of forming all organs in order, and this formed sperm/fertilized ovum has become a self (alive) by the strength of the male's influence on it.

The soul is like being born (generated) from the male sperm, and the body from the female semen "ovum". When this develops the ability to breath (becomes alive), then the soul moves within it towards the completion of the organs. This soul is then a nourishing soul (blood), or it has no other function, even if it has the power to do otherwise.

If the sperm prepares the nourishing power to receive/accept actions intended for the soul. The spiritual aspects of the pronunciation

are of one nature, because the spiritual/rational and vocal organs are formed together in these beings. Nor do the nourishing spirit and its organs apply. Furthermore, the animal's organs are not endowed with spiritual, but rather with the ability to accept food. It is possible that the nourishing soul inherited from the father remains until the *mizaj* undergoes a transformation, at which point the specific nourishing soul joins it.

It seems that the benefit from the father does not reach the ability to complete the planning to the end, but rather it fulfills the planning of what needs a strong origin.

As if the father's semen contributed to the fertilization process has changed from what it should be, then, it is not from the type of absolute nutrient that was in the father and that is in the son.

Be that as it may, if the heart and brain are formed within the body, the rational soul becomes attached to them, and the spiritual soul emanates from them. The rational soul, however, is distinct and immaterial, and it is perfected by something external that benefits the mind/intellect. As for the other faculties, they are perfected through the body and physical matters.

In the semen there is an "essence" that is the first essence that accepts it, this soul is the reason for collecting the semen's parts, and it is the agent of the semen and its maturation, and it is separate in itself. , so if it separated from the semen it becomes decays and decomposed. This soul/essence is a divine body, its relation to semen and organs is like the relation of the intellect to the psychic faculties.

The mind is the best non-corporeal essence, and the soul is the best corporeal essence. This essence does not leave the semen as long as it is correctly and accurately intact in the womb, but rather it transforms the semen into its essence, so it dissolves, becomes refined, and becomes spirit. Then the formed zygote is filled with spiritual wind, and this spirit becomes a penetrating spirit that forms the organs by its faculties, and perfection is achieved for these organs.

* Reference: "The ash-Shfaa" Book of Ibn Sina - Second section "Naturals" Sixteenth article " The Animal Book" the eighth art" 1st chapter: on how an animal is bred from sperm and eggs and the difference of the animal in it. The investigation of Abdul Alim Muntasir-said Zayed-Abdullah Ismail, introduction and review of Ibrahim Medkor - 1970-P.: 401-404-Egyptian General Authority for authorship and publishing.

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