THE DEVELOPMENT OF THE HEART
IN THE GUINEA-PIG (CAVIA COBAYA)

by

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INTRODUCTION

A great amount of study has been done upon the development of the mammalian heart. There has been some work concerning its development in the guinea-pig. Almost all writers are agreed upon its general development although they differ somewhat as to the details.

Purpose

The purpose of this investigation has been to study the method of the development of the heart in the guinea-pig, to compare this with what other workers have done and to relate this to the development of the heart in other mammals.

Review of Literature

According to Kellogg (1928), Galen (about 300 A. D.) gave the first adequate description of the fetal heart. He observed the foramen ovale and ductus arteriosus. Kellogg (1928) mentioned that Sabatier (1798) gave an account of blood flow in embryos which is the prevalent belief today. Pohlman (1909) stated that Harvey (1628) performed some accurate observations upon the adult pulmonary and fetal heart circulation.

According to Yoshinaga (1921), Strahl and Carius (1889) investigated the formation of the pericardial cavity and presence of a ventral mesocardium in the guinea-pig. Later, Yoshinaga (1921) states that Favoro (1913) studied the formation of the atrial septum in this animal. Yoshinaga (1921), one of the latest workers, described the very early heart development in the guinea-pig.

Much work has been done upon the embryology of the human heart. Its development has been worked out from the earliest stages. Some of the more recent workers include: Dandy (1910), Mall (1911, 1912), Tandler (1912), Ingalls (1920), Bartholmez and Evans (1926), and Davis (1927).

Schutlze (1916) described the fusion of the cardiac anlages and the formation of the loop in the pig. Bremer (1928) made an extensive investigation on the complete transformation of several types of hearts including the changes taking place from the fusion of the lateral tubes to the fully formed fetal structure. The formation of the heart in the rabbit was described by Murray (1919). He gave special reference to the formation of the ventricular septum.

Retzer (1908) described the formation of the atrial septum in the pig, man, rabbit and monkey. He mentioned that Rose (1888 and 1889), and Born (1889) made earlier studies of this kind. Thyng (1914) studied the atrial septum formation in the human heart and Morrill (1916) made a complete investigation of this septum in pig embryos. He also described the septum secundum. Recently, Patten (1925), and Chan Chung (1931) have investigated the formation of the atrial septum in chick embryos.

Pohlman (1907 and 1909) and Kellogg (1928) made valuable investigations of the course of blood flow through the fetal mammalian heart and elaborated on the amounts of blood and direction of flow in each division of the heart.

MATERIAL AND METHODS

The animals used in this investigation were obtained through the courtesy of the Animal Husbandry Department. They were kept in steel cages in the basement of a limestone building.

In order to control breeding conditions the males were kept in separate cages. Each day at a regular hour each female showing an open vagina was placed in a cage with a male and observed closely. If a copulation occurred, a record of it was placed in the general record book and also on the female's card. An example of such a record would include: (P-5♀ x P-42♂) 7:30 a.m., December 20, 1932; vaginal plug. Errors were partially eliminated by means of this double check. At this same time each day the animals were fed a balanced ration of alfalfa hay, rolled oats mixture, sprouted oats or green alfalfa and water.

A total of thirty-four females was killed of which only two were non-pregnant. In addition to this material, embryos from thirty different litters, having these same ages, which were prepared by Marjorie (Prickett) Dobrovolny (1930) for a study of the external form of the guinea-pig embryo, were used. Embryos from eleven litters prepared by Dorothea (Dowd) Jewell (1927) in a study of the develop- of the ovary in the guinea-pig, were used.

Procedure

Females of fourteen to twenty-nine days of pregnancy were killed and the embryos removed for study. Before killing a female for dissection all material and instruments to be used were in readiness to prevent delay in getting the embryos into the fixing agent. Illuminating gas was found to be the most successful and convenient means of killing.

As soon as the animal was dead the abdomen was opened and the uterus exposed. A sketch showing the location of the embryos in the uterus was drawn before further dis- section was made. The embryos were removed from the uterus and placed at once into Bouin's solution. In almost all cases the fetal membranes were removed from the embryo before fixation. However, in the smaller ones the fetal membranes were not removed until after staining. The embryos were stained "in toto" in acid alum carmine, im- bedded in paraffin and cut in serial sections varying in thickness from ten to seventeen microns.

Cardboard reconstructions were made of a sixteen day and two hour embryo and a twenty-three day embryo. Hearts from embryos twenty-six, twenty-seven and twenty-nine days of age were dissected out and studied under a binocular microscope.

DESCRIPTION

Variations in Development

According to Harman and Prickett (1932, 1933), there is some difference in degree of development between embryos of the same copulation age. This has been explained by the fact that apparently fertilization does not always occur at a definite time after copulation. We have found this difference in this investigation. We have also found that embryos from the same uterus may differ slightly in the degree of development. The age of all the embryos used in this investigation was calculated from the time of copulation.

Earliest Stages in Development

In the guinea-pig the process of fusion of the heart tubes and formation of the cardiac loop is rapid. The entire formation of the fetal heart takes place between the embryonic ages of fourteen and twenty-nine days. The heart begins its development early in the fourteenth day before the embryo reaches the age of fourteen days and five hours.

In the flat embryonic disc of fourteen days and one hour there are no indications of embryonic blood vessels. The ectoderm of the somatopleure is greatly thickened and is folding up to form the medullary plates. This folding is more developed in the forebrain region. The mesoderm on either side of the midline is beginning to thicken and the first two pairs of somites are forming. The endoderm is spread out flat ventrally. In an embryonic disc of fourteen days and two hours (Fig. 10) the beginning of the myoendocardial tubes can be seen along the lateral edges of the blastoderm. The mesoderm cells of the somatopleure have proliferated in this area and changed in appearance so that they stain more deeply. In many areas these cells have arranged themselves in loosely connected groups and in other more advanced areas a lumen has formed in the center of these groups. These earliest blood cells are connected to one another by small protoplasmic threads. These areas mark the point of origin of the myoendocardial tubes and in general run parallel to the neural tube from the posterior end of the embryonic portion of the blastoderm to the anterior end.

In studying several embryos fourteen days and nine hours old, little change in development is found. This is true of some litters but embryos from other litters show greater development. In those of least development, the endoderm on the ventral side is invaginating to form the notochord. This invagination is almost in contact with the ectoderm of the brain in the region of the midline. There are no mesoderm cells intervening between the ectoderm and endoderm at this point. The pericardial cavity has not made its appearance. In another embryo from the same uterus we find a slight increase in development. The myoendocardial anlages form connected tubes in this stage and reach from the posterior end of the blastoderm to the anterior end. At the posterior end they are widely separated but at the anterior end in the forebrain region they suddenly converge toward the central line. The blood vessels are made up of two tubes; one within the other. The inner, endocardium, will form the lining of the heart and the outer, myocardium, will form the muscular layer of the heart. The anterior ends of these longitudinal vessels are much more dilated than the posterior end. In the mesoderm ventral to the medullary groove are seen scattered cells similar in appearance to those which formed the anlages of the myoendocardial tubes. These cells appear to be proliferating from the somatic mesoderm and are coalescing to form the dorsal aorta. In an embryo of the same age but from another litter the myocardial tubes have fused for a very short distance in the anterior end.

The External Structure of the Heart

Embryos from two litters aged fourteen days and five hours show some advancement in development (Fig. 1). The primitive pericardial cavity forms an open channel on both sides. These channels meet in the forebrain region in a wide open cavity. Within this the heart anlages lie connected dorsally to the mesoderm surrounding the primitive gut by the dorsal mesocardium which is formed when fusion takes place. The endoderm of the splanchnopleure has invaginated to enclose the primitive pharynx. This invagination has been brought about by a ventral folding of the lateral blastoderm so that the heart anlages are carried around in a position ventral to the pharynx. The myoendocardial tubes are not of uniform diameter throughout but are enlarged in some areas and constricted in others. In general there are four main regions of enlargement. Beginning at the anterior end they are the bulbus, ventricular, auricular and sinus venosus. A constriction has formed between each portion so that each enlargement bulges out.

This reduces the lumen to a narrow dorsoventral cleft. In this stage the heart tubes have converged so that they are fused for a short distance in the bulbar region. Figure 1 shows that it is only the myocardial layer which is fused. The portion of the tubes directly posterior to the point of fusion turns almost at right angles and passes directly out into the blastoderm. Anterior to the heart region the ventral aorta is seen connected by the first arch to the dorsal aorta, dorsal to the pharynx. This connection has been found in the earliest stages and has led to the conclusion that these three vessels arise simultaneously. Both the myocardium and endocardium have fused in the bulbar region before the auricular portions of the heart tubes have met. The presence of a ventral mesocardium is doubtful. If present, it remains for only a short time. There is one point however when there is a slight indication of a ventral connection. It occurs at the region of fusion of the tubes and is seen in only a few sections.

An embryonic disc fourteen days and three hours old shows a degree of development in advance of any examined for this age. Here both the myocardial and endocardial tubes have fused in the bulbar and ventricular regions. The auricular portions are still widely separated. By the end of the fourteenth day the heart anlages have almost entirely fused except for occasionally scattered cells between the tubes in a few regions. These soon disappear as complete fusion takes place. In the following ten hours changes occur in rapid succession. The heart tube grows in length much faster than the pericardial cavity in which it lies. This causes the tube to twist which results in the formation of a loop. The forebrain region is bent forward, further restricting the area for extension of the heart tube. The initiation of the loop begins at fifteen days and three hours and is practically completed within eight hours. There are two constrictions formed in the single heart tube. The first, between the bulbus and ventricle, is greater on the right side; the second, between the ventricle and auricle, is greater on the left side. These sulci continue to increase in depth. The heart tube is bent, at first, ventrally and to the right, and then dorsally and to the left so that the auricular region is carried around dorsal and anterior to the ventricular region.

At approximately the same time that the formation of the loop is being completed a lateral enlargement appears on either side of the venous end of the tube. These pouches are destined to be the future auricles. They grow rapidly in size and soon fill up the immediate area, and are then forced to spread out over the bulbar and ventricular portions of the heart (Fig. 6). At this stage the sinus venosus is directly back of the auricular region and the ducts of Cuvier empty into the right and left sides, respectively. In the stage represented by the sixteen day eight hour embryo (Fig. 12) a constriction is being formed between the auricles due to their enlargement. At this time the external structure of the heart is practically complete. The changes that follow will be primarily concerned with growth in size and adjustment.

The Internal Structure of the Heart

The inside of the heart of a sixteen-day embryo is merely one large connected lumen. From this undivided tube will be developed a four chambered heart. The principal changes to be considered are those connected with the formation of the interatrial and interventricular septa. The interatrial septum divides the primitive atrial cavity into the two auricles, and the interventricular septum divides the primitive ventricle into the right and left ventricles. The development of the following structures contribute to the formation of the four chambered heart. The formation of the parts connected with the interatrial septum, the absorption of the sinus venosus into the right auricle, the division of the atrial canals, the formation of the interventricular septum, the division of the bulbus aorta into the pulmonary artery and the aorta, and the formation of the pulmonary veins.

The endocardial tube is dilated in the auricular portion so that it lies in close contact with the myocardium. In the ventricular portion however the endocardium and myocardium are separated by a relatively large space. The auricular portion is a wide open cavity extending laterally into the auricular enlargements. Between the auricular region and the large open ventricle is a narrow neck, the atrio-ventricular canal. The ventricle narrows into the bulbus aorta. The endocardial cushions are the first structures to appear in the internal formation of the heart. These appear about the fifteenth day and third hour as thickenings on the dorsal and ventral margins of the atrio-ventricular canal. The tissue is loosely connected and scattered at first but by the sixteenth day it has acquired a more compact appearance. At this time a definite cushion can be distinguished on each margin but they do not meet. By the seventeenth day these masses have fused mesially to form the right and left atrio-ventricular canals. The endocardial cushion grows slightly dorsally and ventrally and eventually takes part in the separation of the auricle and ventricle. During the formation of the loop the atrio-ventricular canal has been shifted to the left and dorsad to the primitive ventricle.

The myocardium of the ventricle at about fifteen days and nine hours appears thicker and produces anastomasing processes which project into the space between the endocardium and myocardium. This spongy tissue is the beginning of the trabeculae which will take part in the formation of the atrio-ventricular valves and the interventricular septum.

In the heart of embryos sixteen days and two hours the auricles communicate widely. The blood is allowed to pass freely into each one from the sinus venosus. From the auricles the blood passes through the atrio-ventricular canal, through the open ventricle and out the bulbus aorta. In embryos sixteen-days and eight hours old the first structure which will eventually take part in the separation of the auricles appears. It is the septum primum. The septum primum appears as a thickening of the musculature of the anterior dorsal roof of the atrium (Fig. 12) and is continuous with the floors and posterior wall. The outer edge of this thickening is covered by a layer of endocardium which remains intact as the septum grows outward into the atrial cavity. As the septum grows downward it forms an incomplete curtain between the auricles. The blood stream passes under it in going from the right auricle into the left auricle. This passageway, between the septum primum and the endocardial cushion is the primitive foramen ovale. By the time embryos are eighteen days and eight hours old the septum primum is fused with the endocardial cushions. But about this time an opening has appeared in the septum primum. A region near the center becomes thinner and finally breaks through. Now, the blood passes through this opening from the right auricle to the left. This ostium is the permanent foramen ovale and will remain functional until birth.

Following the formation of the loop in the fifteenth day, the sinus venosus is located back of the atria. Early in the sixteenth day the sinus venosus is shifted to the right so that the left horn becomes longer and smaller in diameter than the right. At the beginning of the seventeenth day the sinus venosus is being taken into the right auricle. The first indication of this is the presence of the infolding of the muscular wall of the sinus venosus into the opening of the auricle. These folds appear on the posterior dorsal wall and represent the right and left venous valves as shown in Figure 14. Another spur-like thickening located above the opening but continuous with the venous valves protrudes out with the cavity of the auricle (Figs. 13 and 14). These flap-like structures appear to direct the blood flow into the left auricle, thus preventing its passing into the right ventricle. The thickenings of the right and left venous valves continue to grow and pass along the dorsal atrial wall toward the endocardial cushions. By the nineteenth day and fourth hour the right venous valve has reached this point, but the left venous valve grows much more slowly and during the twenty-first day fuses with the septum primum and the endocardial cushions. A portion of this fold takes part in the formation of the septum secundum. Following the fifteenth day the left duct of Cuvier and left limb of the sinus venosus gradually decrease in size. By the eighteenth day the left duct of Cuvier breaks away and the blood is carried over into the superior vena cava through the innominate vein.

Up to the time that the embryo is eighteen days old the bulbus aorta is an undivided tube. At eighteen days and eight hours the origin of the bulbar septum is seen. It arises as a thickening of the wall of the bulbus on the dorsal and ventral sides. This thickening is continuous on both sides down to the point where the bulbar portion joins with the ventricular portion. Near the ventricular region a thickening has also appeared on each of the sides of the bulbus. These four areas will form the semilunar valves. By the twenty-third day the dorsal and ventral thickenings have met mesially in a few areas thus incompletely separating the bulbus into the pulmonary artery and aorta. In the region nearest the ventricle they have fused. Figures 16, 17, 18 and 19 show the formation of the semilunar valves. By the end of the twenty-fifth day the bulbus is completely separated so that the pulmonary artery communicates with the right ventricle, and the aorta with the left ventricle.

The septum secundum is one of the last structures to appear. In the twenty-third day it is seen as a fold in the dorsal wall of the right auricle in close communication with the septum primum. Its ventral edge is continuous with the left venous valve. By the twenty-seventh day this septum forms an incomplete flap over the foramen ovale. In a dissection of an embryo twenty-nine days old the septum secundum had grown so that it completely overlaped the foramen ovale.

DISCUSSION

There are some differences of opinion as to the manner in which certain details of the heart develop. Schultze (1916) states that in the cat the endocardial tubes do not fuse until the cardiac loop has been completed. In the guinea-pig we find that the endocardial tubes are beginning to fuse at the age of fourteen days and nine hours, thus preceding the formation of the loop which takes place approximately between the ages of fifteen days and three hours and fifteen days and eleven hours.

Yoshinaga (1921) described the formation of the pericardial cavity in the guinea-pig as a fusion of small ventricular intermesodermal spaces. This is essentially the same as we have found in our investigations.

The formation of the cardiac loop as we have found it in the guinea-pig is similar to that found in the cat, Schultze (1916); in man, Mall (1912), Tandler (1912), Ingalls (1920), and Davis (1927); in the chick, Bremer (1928); and in the pig, Patten (1927), and Lewis (1903).

In regard to the formation of the atrial septum, Retzer (1908) states that there is no indication of the septum secundum in the rabbit, human, pig and monkey. Also he states that Born and His (1889) described a second septum, the septum secundum, which arises from the anterior upper wall. This becomes the ultimate auricular septum.

Morrill (1916) confirms the work of Born and His (1889), and states that Favaro (1913), also found a second septum in the guinea-pig. In this investigation, as shown in Figures 8 and 14, we have found a second septum on the right side of the septum primum in the guinea-pig. This confirms the results of Morrill (1916), and Favaro (1913).

Tandler (1912), and Jordon (1926), mention the septum secundum in the human and Patten (1927) shows it in the pig.

Schultze (1916) in working with the cat found the right vitelline vein to be larger than the left and used this fact to aid in explaining the formation of the cardiac loop. He stated that a greater amount of blood flowing against one wall of the heart tube than the other, would tend to push the heart in that direction. Ingalls (1920) and Davis (1927) in studying human embryos disagree with Schultze and state that the left vitelline vein is the larger. Chan Chung (1931) found that the right vitelline vein is the larger in chick embryos. In our investigations with the guinea-pig we have found that throughout the length of these vessels that there are variations in the diameter of each but that in general neither one is larger than the other. The chronological appearance of the chief structures of the heart as we have found in the guinea-pig, corresponds to the chronological summary of the appearance of these structures in the human as given by Jordan (1926).

SUMMARY

1. The formation of the fetal heart takes place between the embryonic ages of fourteen and twenty-nine days inclusive.

2. The heart begins its development at about the age of fourteen days and two hours as a longitudinal blood vessel along each side of the midline.

3. The heart anlages have completely fused by the end of the fourteenth day.

4. The fusion of the myocardium is in advance of the fusion of the endocardium.

5. The initiation of the loop begins at about the fifteenth day and third hour, and is practically complete after eight hours.

6. The auricular enlargements appear at about fifteen days and nine hours.

7. The septum primum begins as a spur-like projection into the auricular cavity at about sixteen days and eight hours. The septum spurium is first seen about five hours later. The ventricular septum begins about the same time as the auricular septum.

8. The endocardial cushions make their appearance about the fifteenth day and eighth hour, and at seventeen days they are fused mesially.

9. Indications of the bulbar septum are first seen at eighteen days and eight hours.

10. At twenty-five days the ventricular septum has fused with the endocardial cushions and the bulbar septum.

Thus they separate the right and left ventricles, and the bulbus aorta into the pulmonary artery and the aorta.

11. The septum secundum begins on the twenty-third day; it nearly covers the foramen ovale at the twenty-fifth day and by the twenty-ninth day it has extended over this opening.

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EXPLANATION OF PLATES

The outlines for the drawings were made with the aid of a microprojector apparatus.

PLATE I

Fig. 1. Fourteen day five hour embryonic disc showing the early heart anlages. X59. PC, pericardial cavity; B, bulbus; V, ventricle; A, auricle; E, endocardium; M, myocardium; VV, vitelline veins.

Fig. 2. Fifteen day two hour embryo, showing the heart anlages fused into a single tube. X41. B, bulbus; V, ventricle; A, auricle; S, sinus venosus; VV, vitelline vein.

Fig. 3. Fifteen day four hour embryo, showing formation of the cardiac loop. X59. V, ventricle; B, bulbus.

Fig. 4. Sixteen day one hour embryo, showing further development of the cardiac loop. X48. B, bulbus; V, ventricle.

Fig. 5. Seventeen day embryo, showing a little further development. X47. B, bulbus; AV, atrio-ventricular canal; V, ventricle.

PLATE I.

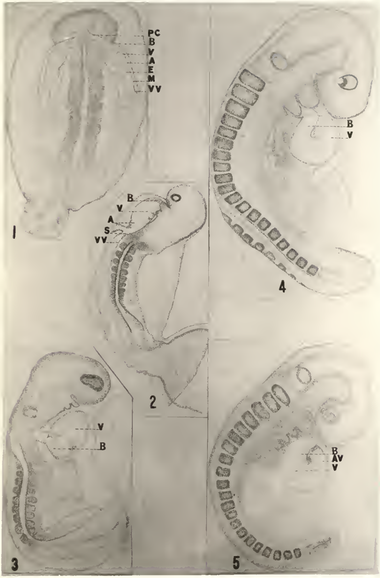


PLATE II

Fig. 6. Ventral view of a heart from a twenty-three day embryo. X50. RA, right auricle; LA, left auricle; DA, ductus arteriosus; AO, aorta; RV, right ventricle; LV, left ventricle.

Fig. 7. Ventral view from the left of a heart from a twenty-seven day embryo. X50. RA, right auricle; AO, aorta; RV, right ventricle; LV, left ventricle; LA, left auricle.

Fig. 8. Ventral view of a heart from a twenty-seven day embryo with the right auricle open showing arrangement of the parts. X50. SVC, superior vena cava; SI, septum primum; FO, foramen ovale; SII, septum secundum; RVV, right venous valve; PA, pulmonary artery; LA, left auricle; LV, left ventricle.

Fig. 9. Right lateral view of a heart from a twenty-seven day embryo with the right ventricle open showing tricuspid valves. X50. IVC, inferior vena cava; SVC, superior vena cava; TV, tricuspid valves; RV, right ventricle; LV, left ventricle.

Fig. 10. Transverse section through the anterior region of a fourteen day two hour embryonic disc, showing early formation of vitelline veins. X130. AC, amniotic cavity; NF, neural fold; VV, vitelline vein; N, notochord.

Fig. 11. Transverse section through the heart region of a fourteen day five hour embryonic disc, showing fusion of myocardium. X130. DA, dorsal aorta; G, foregut; PC, pericardial cavity; E, endocardium; M, myocardium.

Fig. 12. Transverse section through the heart of a sixteen day eight hour embryo, showing origin of septum primum. X48. SI, septum primum; A, auricle; V, ventricle.

Fig. 13. Transverse section through the heart of a seventeen day one hour embryo, showing origin of septum spurium. X42. A, auricle; SS, septum spurium; V, ventricle.

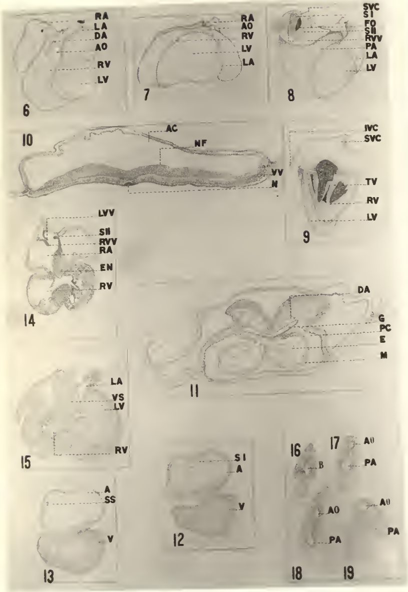
Fig. 14. Transverse section through the heart of a twenty-three day embryo, showing incomplete separation of ventricles and arrangement of auricular valves. X54. LVV, left venous valve; SII, septum secundum; RVV, right

venous valve; RA, right auricle; EN, endocardial cushion; RV, right ventricle.

Fig. 15. Transverse section through the heart of a twenty-five day embryo, showing complete separation of ventricles. X54. LA, left auricle; VS, ventricular septum; LV, left ventricle; RV, right ventricle.

Figs. 16, 17, 18, 19. Transverse section through the bulbus of a twenty-three day embryo, showing formation of the semilunar valves. X54. B, bulbus; AO, aorta; PA, pulmonary artery.

PLATE II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