

GROSS DIFFERENTIATION OF THE HEART
IN THE BOVINE AND HUMAN

by

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INTRODUCTION

The structure and many frailties of the adult human heart have become well known (Robb, 1965), general structure of the bovine heart (Sisson, et. al. 1953), and early stages of the heart development have been studied (Noden, 1965), but the structure or rate of growth of the heart of mammalian fetuses have received no attention. The nearest approach to a study of the fetal heart has been made with the study of changes at birth (Arey, 1954; Patten, 1958; Lind, et. al. 1964).

Normal development of an organ is, in itself, of considerable interest to any developmental anatomist, but a knowledge of normal development becomes essential as a basis for teratology. With the present emphasis on congenital malformations and teratologic effects of various drugs, anatomists have found themselves extremely short of basic information as to how the heart, and other organs, develop, when and how basic changes occur, and what can be considered as departure from normal.

As I had developed a definite interest in teratology, particularly cardiac teratology, the lack of basic information became critical. The emphasis at Kansas State University on bovine embryology afforded an opportunity to coordinate a study of heart development with other studies in progress. Luckily a few human fetuses were available for dissection and comparison.

In consideration of the needs and opportunities, a series of studies was devised to learn first hand and describe normal fetal development of the heart, acquire data for growth charts, and compare bovine and human heart development.

LITERATURE REVIEW

The early development, and fusion of the primordial vessels to form the heart, is parallel in the bovine and the human (Noden, 1965). In the human, fusion of the paired endocardial primordia extends throughout their entire length by 28 days, and the regional divisions of the heart become delimited (Kramer, 1942).

The division of the atrium into two chambers begins with the septum primum growing from the mid-dorsal wall of the atrium toward the ventricle and fusing with the endocardial cushions, obliterating the previous free communication between the right and left halves of the atrium. The septum primum becomes thinned and perforated in a previously intact region, forming the interatrial foramen, thus, there is at the end of the sixth week a separate right and left atrial chamber (Arey, 1954). In the seventh week the septum secundum is an incomplete membrane, its prominent aperture being known as the foramen ovale. The main expense of the septum primum overlaps the foramen ovale and serves as a valve. This condition is maintained until the equalization of pressures in the two atria permits the septa to lie in constant apposition and so unite into a joint atrial septum (Arey, 1954). The division of the atrium and formation of the interatrial foramen described by Noden (1965) for the bovine is basically the same as Arey (1954) described for the human.

The formation of the paired atrial and ventricular chambers and their valves is based on the development of an endocardial cushion. Its initial formation was described by Kramer (1942) as an increasing number of mesenchymal cells invading the "cardiac jelly" and differentiating into a primitive connective tissue.

In the human embryo of less than 4.3 mm the posterior (dorsal) cushion reached nearly to the sinus venosus but not as far into the left ventricle or the atria as does the anterior (ventral) cushion. The anterior cushion inserts on the medial side of the opening from the sinus venosus, and the superior septum (primum) and the septum of the ventricles (septum inferius) are beginning to form (Mall, 1913). The dorsal and ventral atrio-ventricular canal cushions rapidly increase in thickness and width (Kramer, 1942). In the 8-9 mm human they are quite broad, and each cushion exhibits a tubercle at each of its lateral borders, which, dividing the atrioventricular channel into a right and left channel. The final division of the common channel is accomplished by the merging of endocardial cushions of the atrio-ventricular canal (Kramer, 1942). The division of the atrio-ventricular foramen was underway in the 35 somite bovine embryo by formation of interatrial septum and endocardial cushion (Noden, 1965).

Three time periods in the formation of the valves in humans has been postulated by Odgers (1939): (1) in embryos from 11.2-23 mm the valve cusps have two distinct components, the cushion tissue and the muscular trabeculae of the ventricular wall, of which the former is the most prominent; (2) in hearts of 28.5-61 mm embryos the cusps are essentially muscular with remains of the cushion tissue on their auricular aspect; and (3) 85 mm-term the muscle in the cusps is replaced by collagenous tissue.

According to Mall (1913) the two endocardial cushions give rise to the medial cusp of the tricuspid valve and the anterior cusp of the mitral valve. Complete

union of the cushions obliterates foramen ovale I. Foramen ovale II is well above the common fibrous process of the united cushions.

Odgers (1939) stated that the right cusp of the mitral valve becomes muscularized on its ventral border by muscular chordae which appear to split and grow along both its ventricular and auricular aspects, while muscle fibers from the left border of the muscular inter-ventricular septum were investing the ventricular surface of the cusp in its dorsal portion. The left cusp is composed almost entirely of muscle. During the same period the right cusp of the mitral valve could be recognized as a well-marked structure, formed by the left extremities of the superior and inferior tubercles.

Mall (1913), stated that in the first time period of Kramer, the most definite valve was the anterior cusp of the mitral, formed by the union of the left lateral tips of the anterior and posterior endocardial cushions, each tip bound to the trabecular system by well formed muscle strands.

Mall (1913) stated that the septum aorto pulmonale blends with the cushions of the tricuspid valve through a dorso-lateral wing which is divided into two branches. The right bulbar ridge grows across the tricuspid orifice and joins by its left border the fused atrio-ventricle cushions, while its free margin bulges ventrally and overhangs the caudal portion of the tricuspid opening to persist as the cushion of the anterior cusp of this valve. The right bulbar ridge is thus responsible for the formation of both the anterior and the right, or posterior, cusps of the tricuspid valve (Odgers, 1939).

The medial cusp of the tricuspid valve is attached in front by the medial

tendon, and behind by the large papillary muscle, and the inequality of these two structures accounts for the double appearance of the lateral valve. Mall (1913) stated that:

"In reality no true tricuspid valve is present and correctly speaking there is no tricuspid valve. Both are bicuspid with medial and lateral cusps. Both are tied down by two muscles, the two papillary muscles on the left side and the large papillary muscle and the median tendon on the right side."

Bayne-Jones (1917) found the heart valves and chordae tendineae of humans to be supplied with blood vessels. The tricuspid and mitral valves receive arterioles from the annular branches of the right and left coronary arteries, which undergo multiple branching, forming tufts of vessels throughout the valve. The vascularity of the chordae tendineae is slight, with arteries derived from the coronary artery branches which supply the papillary muscles. Nearly all the vessels in the chordae lie just beneath the endothelium, but some are situated in the center of the chordae.

Division of the ventricles begins with the formation of the interventricular septum by the beginning of the second month. The septum appears to grow from the apex to the base, but more accurately, the cavities grow down leaving the intervening wedge of muscle as the interventricular septum. This septum is usually complete by the end of the second month (Robb, 1965). The closing tissue, septum membranaceum, is formed of connective tissue derived from the upper margin of the muscular interventricular septum, the endocardial cushion and the conus ridges (Robb, 1965). The remaining portion of the original septum is the septum musculare (Arey, 1954).

The developing mitral and tricuspid valves are connected to the walls of the ventricle by stout muscular bands. Each band is derived from trabeculae of the ventricular wall, reaches the cushion above and below the left atrio-ventricular orifice and spreads over it, thus forming the anterior and posterior papillary muscles (Odgers, 1939). The moderator band originates just below the medial cusp of the tricuspid valve, but in its further development it shifts towards the apex where it bands the large papillary muscle with the extension of the crista supraventricularis (Mall, 1913). In their course from the valve to the outer wall of the heart the papillary muscles communicate continuously with the trabecular system.

The anterior papillary muscle arises from the right wall of the ventricle and is joined at its lower border to the septal wall, and inserts on the anterior and lateral cusps. The posterior papillary muscle comes from the septal wall and joins by its chordae musculares to the lateral cusp (Mall, 1913).

The development of the ventricles and the papillary muscles in the bovine was most thoroughly covered by Noden (1965). Myocardial cells displace endocardial jelly in longitudinal ridges within the ventricular wall. Trabeculae form by the expansion of the ridges of myocardial cells and by evagination of endocardium into the spaces between. Most of the bands are longitudinal within the ventricle, attached at both ends, and nearly separated from the lateral wall by continued undercutting of the endocardium. The cardiac jelly continues to be reduced and the trabeculae are well developed by the 29 somite stage. By 30 somites, a definite interventricular septum at the posterior tip of the ventricle was observed and there was an indication that moderator bands began to

develop by 35 somites. The inter-ventricular septum was well formed in the tip of the ventricle, extending anteriorly along both the ventral and dorsal walls. Other chordae tendineae may arise from the septal wall, muscular ridges, or papillae located peripheral to the septum or dorsal cusps.

Trabeculae carneae run from the base to the apex of the ventricle and converge there, forming muscular columns or pillars (Miller, et.al.1964). The presence or absence of the trabeculae septomarginalis (Moderator band) is dependent on the position of the anterior papillary muscle of the right ventricle. In function the moderator band is important only in so far that it contains the right branch of the conductive system (Retzer, 1909).

Shaner (1963) described the semilunar valves as rising from four endocardial cushions within the distal end of the bulbus. Two of the cushions are large and cap the long spiral bulbar ridges; the other two are small, short, intercalated cushions. Although all six cusps appear at the same time, their sinuses do not deepen at the same rate. The coronary arteries are associated with the right and left cusps of the aortic valves. In the pulmonary artery, the left and the anterior cusps are large and equal, but the right cusp is small. In the aorta, the two coronary cusps are large and equal, but the posterior cusp lags behind the rest. Differences in early cusp development are due to the peculiar configuration of the pulmonary and aortic blood streams preceding the closure of the interventricular foramen. The two larger left and anterior pulmonary cusps lie on the outer aspect of this spiral stream; they are more affected by the ebb and flow of the blood, and their sinuses are deepened thereby. The aortic blood stream flows a fairly straight course, but it has another ebb from the two

coronary arteries which stimulates the faster growth of the two coronary aortic cusps.

The heart muscle receives blood from the coronary arteries, which arise long after the embryo has a workable circulation. The vessels of the cardiac-coronary system arise by endothelial budding, first appearing as sprouts from endothelium of the ascending aorta or the coronary sinus along with that small portion in the few Thebesian vessels incorporated into the system.

There has been much controversy about the amount and type of blood which flows through the foramen ovale of the embryonic heart. The earliest theory and one which many people now believe was stated by Sabatier (1791). Patten had this to say about the theory:

"The striking thing is the persistence of the Sabatier doctrine that the entire inferior caval blood stream passes directly through the foramen ovale to the left atrium, while the superior caval blood passes with little or no mingling into the right ventricle."

Licata (1954) concurred somewhat in this theory, as shown by his description of the blood flow into the artia. The vena cava and coronary sinus open into the atrium making it the common entrance for the venous blood from the systemic, portal and placental circulations. The two atria are approximately equal in size, indicating that they accommodate comparable amounts of blood. The inferior vena cava is so oriented that its stream is directed toward the foramen ovale, so it is the dominant source of the equalizing flow to the left atrium. In human hearts of 9 weeks the stream from the inferior vena cava impinges on the ventral pillar of septum secundum and is probably divided into two streams. The right venous valve is highly developed at this stage, and the

left venous valve has been considerably reduced. As a result there is a deep sinusal bay of the right atrium between the right venous valve and the interatrial septal complex into which all the major veins empty. The morphology of this region suggests that a considerable part of the inferior caval stream passes directly through the interatrial "functional orifice" into the left atrium. The right venous valve may well act as a baffle helping to insure adequate charging of the left atrium.

Arey (1954), Patten (1958), and Lind, et.al. (1964) all considered that equalization of pressure in the left and right atria resulting from increased flow of blood through the lungs after birth, causes the valve of the foramen ovale to become unused and this functionally closes the foramen. Morphological closure of the valve is caused by the gradual fusing of the septum primum with the margin of the foramen ovale. Although closure is usually complete after about the first year, more than 20% of all individuals never obtain perfect closure.

The closure of the ductus arteriosus is generally considered to occur soon after birth but according to Arey (1954), Patten (1958), and Lind, et.al. (1964) this is not accomplished until the sixth to eighth week after birth. Arey described the closure as occurring by proliferation of pads of fibrous tissue into the lumen and thus almost closing of the ductus by one month. Patten (1958) interpreted that the closure of the ductus is accomplished by circular muscle contraction with sufficient force to shut off blood flow during the 6 to 8 weeks needed for morphological closure.

Specific description of fetal heart structure or rate of growth have not been

found in the literature, although it is known that Patten has done considerable work with the human fetal heart.

MATERIALS AND METHODS

Most of the bovine hearts used for this study were obtained from Armour & Co. and Rodeo packing plants in Kansas City, Missouri. The embryos were aged on a growth chart which had been compiled from embryos of known ages. Some of our material was of known ages from the Kansas State University dairy herd.

The human material used for this study was taken from a collection of human fetuses which had been accumulated in the Kansas State University Department of Zoology over the past 20 years.

Measurements were taken with calipers calibrated to tenths of a millimeter. Gross weights were taken on a triple beam balance and small organ weights on a Mettler analytical balance. The "length" of the hearts was taken as the greatest measurement from the base to the apex; "thickness" as the least distance across the outer ventricle walls, and the "width" as the greatest thickness across the ventricle walls. Weights of the hearts were taken to the nearest 0.01 gm after all blood had been washed out and the excess water removed on filter paper. These data were then compiled and growth charts were prepared from it.

The main arterial trunks were severed just below the ductus arteriosus. The hearts were opened by inserting sissors into the aorta and making an incision through the ventricle wall close to and parallel with the interventricular septum.

Another incision was then made through the atrio-ventricular valve into the atrium, leaving the chordae tendineae connected to the valve cusps. The right ventricle and atrium were incised by a comparable procedure. The heart was then opened for careful examination and photography.

The following observations were made on each of the hearts dissected; number of chordae tendineae and papillary muscles associated with the mitral and tricuspid valves; thickness of the ventricular walls; dimensions of the moderator band; condition of the semilunar valves and position of the coronary arteries in association with the aortic semilunars; size and condition of the foramen ovale and its associated valve; inside and outside diameter of the ventricles; size of the coronary sinus opening into the right atrium; and the position of origin of the papillary muscles.

Hearts of various ages were photographed before and after dissection for permanent records. Some hearts were sectioned at 10 microns for microscopic study.

OBSERVATIONS AND DISCUSSION

Anatomy of a Fetal Heart, External Structures

The fetal bovine heart of 66 days is distinctly triangular, from a dorsal view, with the ventricles constituting the apex, and the two atria making up the base (Fig. 1). The ventricles are a firm, heavy walled, conical mass, with the base of the cone against the atria, which are thin-walled, globular structures, separated medially by the interatrial septum.

The right atrium, from dorsal view, appears to be a near globe, flattened posteriorly against the ventricle and medially against the left atrium. The smoothness of the surface is broken only by two or three slight bulges over the atrio-ventricular septum, and the entrance of the caval veins on the dorso-medial aspect. The orifices of the anterior and posterior venae cavae are nearly medially located, antero-posteriorly, and are separated only by a 1.5 mm septum, mostly sinu-auricular node. The beginning of an auricle protrudes slightly to the right overlaying the top of the ventricle.

The left atrium is bordered posteriorly by the ventricle and medially by the right atrium. Extension of the left auricle posteriorly over the lateral surface of the left ventricle disrupts the globular outline of the atrium. Four pulmonary veins penetrate the dorsal surface of the left atrium: two right pulmonary veins near the interatrial septum, far anteriorly, and two left pulmonary veins slightly to the left.

The ventricles constitute approximately two-thirds of the dorsal aspect. The two ventricles are visibly separated by the interventricular septum which is continuous anteriorly with the interatrial septum, and spirals posteriorly to the right, leaving the left ventricle only continuing all the way to the apex. The interventricular septum appears as a depressed line along which course the middle cardiac vein and the dorsal interventricular branch of the left coronary artery. Anteriorly, the ventricles are sharply limited from the atria by a deep groove, in which lie the circumflex branch of the left coronary artery and the great coronary vein. The right ventricle is slightly expanded at its apex beyond the interventricular septum.

From the ventral aspect (Fig. 2) the fetal heart is distinctly subdivided into four parts. The right atrium appears small, completely separated from the left atrium by the pulmonary and aortic trunks. The sharp demarcation of atrio-ventricular septa separates each atrium from its respective ventricle. No vein orifices are visible from the ventral view. The interventricular septum is much more distinct than it was on the dorsal surface, and is more positively spiralled to the right, cutting off the right ventricle far short of the apex. The right ventricle from this side looks rhomboidal in general outline, while the left ventricle is more trapezoidal. The left coronary artery runs from the base of the left atrium to the tip of the right ventricle, branching along the way to both ventricles. With the artery is the coronary vein which receives blood from the ventricular walls on both sides as well as from the interventricular septum.

Internal Structures

Right atrium. The internal aspect of the right atrium has five orifices. The precaval vein opens from the antero-dorsal surface close to the interatrial septum. The large orifice of the interatrial septum is the foramen ovale opening into the left atrium and providing a by-pass for the blood from right to left. Dorsal and lateral to the foramen ovale is the opening of the postcava, directed toward the foramen ovale. The coronary sinus opens immediately posterior to the postcaval orifice and postero-lateral to the foramen. The right atrio-ventricular orifice is guarded by a tricuspid valve, the cusps of which are composed of fibrous connective tissue and arise from the fibrous ring of cardiac skeleton around the orifice (Robb, 1965).

The central portion of the right atrium has a smooth surface, with no trabeculated muscle and is lined by a thin fibrous sheath (Fig. 3). The portions of the atrium which surround the central cavity and overlie the ventricle, have trabeculated muscular ridges, from the fibrous ring of the heart skeleton, over the anterior surface of the atrium, inserting in the fibrous ring on the opposite side. A number of the trabeculae insert directly in the anterior surface of the atrium. Between the trabecular ridges are shallow grooves, formed by the differentiation of the ridges. The atrial wall of these grooves is extremely thin.

Left atrium. The main chamber of the left atrium has six orifices. The four pulmonary veins enter from the antero-dorsal surface just lateral to the inter-atrial septum. The foramen ovale, enters through the postero-dorsal portion of the inter-atrial septum and is covered on the left surface by the valve of the foramen ovale (Fig. 5), presumably the septum primum, which is fused with the septum for approximately three-fourths of its distance around the foramen. There is no fusion over the ventral one-fourth of the foramen, thus leaving an opening for blood passage from right to left, illustrated in an older heart in Fig. 12. The atrio-ventricular orifice is guarded by the mitral or bicuspid valve. The two cusps of this valve arise from the fibrous tissue of the heart skeleton which lies between the atrium and ventricle (Robb, 1965). The cusps of the valve are composed of tough connective tissue and their free edges join with chordae tendineae of the ventricle.

The main chamber is void of any trabeculated muscles, its surface is smooth and lined by a thin fibrous sheath. The auricle and other secondary

chambers around the ventricular edge of the atrium have trabeculated muscle. These trabeculae arise from the fibrous connective tissue surrounding the atrio-ventricular orifice and insert on the fibrous ring of the opposite side. The trabeculae give support to the atrium when it is filled with blood and act as a contracting force to push blood into the ventricle.

Right ventricle. The wall of the right ventricle is approximately 1 mm thick at 66 days, and is deeply cut by grooves formed by regional evaginations of endocardium for approximately one-fourth of this thickness (Fig. 3). These grooves are formed from differential growth of the trabecular muscle ridges which branch and anastomose over the interior of the ventricle wall (Noden, 1965). Locally, the trabeculae enlarge, forming the ventral, medial, and dorsal papillary muscles (Odgers, 1939). These papillary muscles each give rise to 5-6 chordae tendineae which branch many times and insert on the free edge of their respective valve cusps (Odgers, 1939). The chordae are composed of tough connective tissue, and prevent the valves from everting into the atrium upon the systolic beat of the heart. Variable numbers of accessory chordae arise from the trabeculae, septal wall, or ventricular wall and insert on the ventral surfaces of the valve cusps.

Another type of enlarged trabeculated muscle, the moderator bands (Fig. 7), connects from the septal wall, across the cavity and inserts on the opposite wall of the ventricle (Noden, 1965). A large moderator band 2 by 0.5 mm extends across most fetal hearts, from the medial border posterior to the medial papillary muscle diagonally posterio-laterally to the lateral body wall between

the bases of the ventral and lateral papillae. A single band was regular, more than one was not found. A partial function of this band is to prevent the over stretching of the ventricle, but the main function is to carry the right branch of the conductive system (Retzer, 1909).

Left ventricle. The left ventricle is the larger of the heart ventricles. The wall is about 1 mm thick at 65 days, and has trabeculated muscles which form a vast network, by anastomosing and branching over the interior surface, quite comparable to that found in the right ventricle (Fig. 11).

Two of the trabeculae are enlarged, forming the papillary muscles. Each papillary muscle gives rise to 5-7 chordae tendineae, which branch after their origin and insert on the free border of the bicuspid valve. Each papillary muscle, by way of its chordae tendineae, is attached to one of the cusps, the dorsal papillae attaches to the dorsal cusp and the ventral to the ventral cups. There is no crossing of chords. Several accessory chordae arise from trabeculae or the ventricle wall and insert on either cusp of the valve.

In very young hearts an interventricular foramen is present, but is not normally present from 60 days to birth (Robb, 1965) and none was found in any bovine fetal heart. Therefore, the aorta is the only exit from the ventricle. The orifice of the aorta is composed medially by the interventricular septum, dorsally and ventrally by the ventricle wall, and laterally by the ventral cusp.

The semilunar valves. The semilunar valves at the base of the pulmonary trunk consist of three cusps, the dorso-lateral, medial, and ventro-lateral, each cusp is triangular, with two sides attached to the wall of the vessel and the free border farthest up on the artery. A small thickened area of fibrous tissue

at the free border of each cusp insures perfect closure and reduces the friction and wear on the cusps. Small sinuses are formed between the vessel wall and the membrane of the valve, thus preventing the valves from adhering to the vessel wall during systole.

The aortic semilunar valves are also composed of three triangular cusps, with fibrous tissue at the apex of each cusp. The essential difference between the pulmonary and aortic semilunar is the presence of the coronary artery orifices behind the medial and dorso-lateral cusps of the aortic valve. The coronary openings are located at the base of the sinus in close relation to the origin of the cusp. Functionally the cusps divert blood into the vessels during the diastolic phase of the heart beat (Fig. 6).

The pericardium. The pericardium is a tough fibrous tissue which is composed of two layers, the visceral pericardium, which is continuous along the epicardium of the heart muscle, and the parietal pericardium. The parietal pericardium attaches to the vessels of the heart just above their connection with their respective parts of the heart forming a ring around the pulmonary veins and another separate ring around the caval veins and the two aortic trunks. A small sinus, the transverse sinus, is formed between the pulmonary veins and the aortic trunks. Presumably this pericardium forms some type of protective covering for the heart (Miller, et.al. 1964).

Details of the embryogenesis have not yet been determined, but by 64 days the pericardium of the bovine heart has been completely formed and changes only by enlargement after this time.

Course of blood through the fetal heart. The blood flows into the right atrium via the pre- and postcaval veins and coronary sinus. A major portion of the postcaval blood is directed into the left atrium via the foramen ovale, and is prevented from returning by the valve of the foramen. Blood from the precava and coronary sinus, and part from the postcava passes directly through the atrio-ventricular foramen into the right ventricle.

The blood in the right ventricle is then forced out through the pulmonary trunk. A portion of this blood passes into the pulmonary arteries and flows to the non-functional lungs. The remainder is routed through the ductus arteriosus to the descending aorta.

The blood from the lungs returns to the heart through the pulmonary veins to the left atrium. In the left atrium it is mixed with the blood from the right atrium, which flows through the foramen. The blood then moves into the left ventricle and out the aorta. A portion of this blood flows through the brachio-cephalic artery and the remainder to the descending aorta. The blood again returns to the right atrium via the pre- and postcaval veins.

The coronary circulation begins with the blood flowing into the coronary arteries behind the medial and dorso-lateral cusps of the aortic semilunar valves. The blood then flows through the right and left coronary arteries and into the arterial branches along the interventricular septum to branch throughout the ventricles. It returns from the ventricles via the coronary veins, empties into the coronary sinus, and then to the right atrium.

Except for the controversy over the source of blood that passes through

the foramen ovale, there has been general agreement on the course of blood through the fetal heart (Patten, 1954; Miller, 1964; Lind, et. al., 1964).

Anatomical Changes from 66 Days to Birth

General appearance. The atria do not grow at the same rate as the ventricles and by 195-280 days they comprise approximately one-fourth of the exterior aspect of the heart (Fig. 8). The atria of the 90 day heart appear to be expanding at a rate comparable with that of the ventricles (Fig. 8b). The left atrium overlies the ventricle for approximately one-third of its length. The trabeculae are still distinct, even externally, but as the atrial walls become thickened they become indistinct by 132 days and by 195 (Fig. 8c&d) portions between the trabeculae are no longer noticeably thin.

Progressive changes in the shape of the atria also occur. By 280 days the atria are no longer globe shaped, but the right atrium has taken on a trapezoidal with the left medial portion continuing to the interatrial septum (Fig. 10). The main portion of the left atrium is no longer visible from the dorsal aspect and the position it occupied in the 65 day heart is now occupied by the entrances of the pulmonary veins. One of the right pulmonary veins has shifted medially and is separated from the postcava only by the interatrial septum. The other right pulmonary vein has shifted downward and, with the two left pulmonary veins, enter a common chamber that protrudes anteriorly from the middle of the dorso-anterior surface of the atrium.

The orifices of the pre- and postcaval veins are greatly enlarged and are

now separated by a distance of 28 mm. The orifice of the precava has shifted anteriorly and opens directly dorsally. The postcaval opening is directly above the atrioventricular septum.

The right and left atria are separated on the ventral aspect by the enlarging pulmonary trunk and by 280 days they are 26 mm apart. From a slightly left-ventral view, the left atrium has a rather triangular shape. Small projections from the atrium still cover a portion of the ventricle base.

The ventricles increase greatly in length and thickness from 65 to 280 days, 10x6 mm to 140x68 mm, respectively. The definite spiralling of the ventricles of the 65 day heart is still distinct in the 90 day heart, but by 132 days has begun to decline and by 280 days is slightly noticeable (Fig. 8). The left ventricle at 280 days still surpasses the right in length and comprises the apex of the heart (Fig. 11).

The vessels surrounding the atrio-ventricular orifice are no longer visible because of the fat deposits on them. The vessels coursing over the interventricular septum have also become less noticeable with the increase in age. There is little fat deposited on them at 132 days (Fig. 8), but by 195 days the fat is being deposited and by 280 days the vessels are all but obscured by the fat deposits (Fig. 10).

Right atrium. The internal aspect of the right atrium changes considerably with increasing age. The precaval orifice has shifted medially and opens directly along side the interatrial septum by 280 days. The foramen ovale has also shifted from its former medial position to a more postero-dorsal position. The anterior wall of the atrium and the antero-ventral portion of the interatrial

septum form a type of barrier to the precaval blood. With the shift of the foramen and a posterior shift of the postcava, the two orifices are directly opposite. The orifice of the coronary sinus opens immediately posterior to the postcava and ventro-posterior to the foramen ovale. The atrio-ventricular orifice has enlarged progressively with the growth of the heart and the rim has become more fibrous. The tricuspid valves have become more fibrous with age and increased in size. The lateral vein of each cusp now outlines the triangular shape of the valves with the thickened portion at the base and thinning out at the apex of the cusp. Three cusps may definitely be observed as opposed to the description by Mall (1913) who reported that appearance of tricuspid valve resulted from partial subdivision of one of the cusps of a bicuspid type valve.

The opening of the foramen ovale increases from 1 mm at 65 days to 20 mm at 222 days then decreases again to 15 mm at 280 days, apparently in preparation for closure a few weeks after birth. The coronary sinus increases from 0.3 mm diameter at 65 days to 11 mm at 280 days and will continue to increase until the mature heart size is obtained.

The only portion of the atrial wall which is void of trabeculated muscle at 280 days is the interatrial septum. Development of the trabeculae continues throughout fetal life, becoming enlarged myocardial ridges which cover all but a small portion of the atrial wall surface. The grooves between the trabeculae occupy much less of the surface than they did in the 65 day heart, and now cut to one-half the atrial wall thickness. By 280 days few of the trabeculae course the entire atrial surface without inserting many times in the surface.

The secondary chambers surrounding the main atrial chamber are practically filled with myocardial ridges by 280 days. This displacement of chamber space progresses with the increase in age of the heart.

Left atrium. The left atrium has developed into a large irregular organ with an auricle projecting postero-lateral from the margin and orifices more medially. Three pulmonary veins enter a common chamber that protrudes from the antero-dorsal surface and the other enters directly dorsal to the foramen ovale and passes blood across the valve of the foramen, which possibly may enhance closure of the valve. The dorso-lateral shift of the foramen and excessive enlargement of the septum primum from 66 to 280 days results in a small cavity surrounding the valve of the foramen, into which the antero-medial right pulmonary vein empties. The valve of the foramen has greatly enlarged and has fused with the interatrial septum to the extent that approximately one-eighth of the original foramen remains open for blood passage. The valve itself is larger than the foramen and there is some surplus valve tissue which seems to be forming more chordae tendineae. The average number of chords of the valve is 3, the 280 day heart had 5 chords attached to the septum and 4-5 intertwined among themselves (Fig. 11). A portion of the surplus valve tissue seemed to be degenerating (Fig. 12).

The atrio-ventricular orifice has also progressively increased in size with the growth of the heart. The orifice is guarded by the bicuspid valve, the cusps of which are highly fibrous at their bases and decrease in thickness toward their free edge.

The main wall of the left atrium is considerably different than that of the right in the 280 day heart. The wall of the chamber is smooth and free of any trabeculated myocardial ridges. The trabeculae of the smaller surrounding chambers, however, have greatly increased in size, branching many times and inserting at numerous points on the anterior wall. The grooves formed between the trabeculae cut into the atrial wall one-half of its thickness. The entire inner surface of the atrium is lined by a thick, 0.5 mm, tough connective tissue sheath, which is continuous with the valve cusps (Fig. 11).

Right ventricle. The interior of the ventricle enlarged from 5 to 70 mm in length and the exterior increased from 5 to 85 mm. The thickness of the ventricle wall increased from 1 mm at 66 days to 16 mm at 280 days.

The trabeculated muscles in the wall are numerous but many of them anastomose by 280 days. Individual trabeculae were most noticeable along the interventricular septum. Most of the grooves between the trabeculae were being filled by the invasion of muscle cells and the fibrous sheath. A few of the trabeculae extended along the ventricle wall to the semilunar valves.

The papillary muscles increase in size proportional to the heart growth. The chordae tendineae associated become increasingly tough and white. The average number of chordae for the right ventricle is 15 (table 1). The chordae differentiate greatly during aging. In the 66 day heart, the ends attached to the free border of the valve are webbed with a loose connective tissue between the branches of the chordae, but as the hearts aged this material disappears and the discrete branches develop.

Table 1: Number of chordae tendineae in bovine hearts.

| Left ventricle | | Right ventricle | |
|-----------------|--------------|-----------------|--------------|
| hearts counted* | number cords | hearts counted* | number cords |
| 10 | 10 | 15 | 15 |
| 15 | 13 | 13 | 12 |
| 9 | 12 | 12 | 13 |
| 9 | 11 | 5 | 17 |
| 9 | 8 | 4 | 16 |
| 2 | 9 | 2 | 11 |
| 2 | 15 | 1 | 9 |
| 1 | 18 | 1 | 10 |
| 1 | 19 | 1 | 20 |
| 1 | 20 | 1 | 23 |
| | | 1 | 24 |

*Hearts on which accurate information could not be obtained were omitted.

Only one heart examined had more than three papillary muscles in the ventricle. This heart had four; the fourth arose from the lateral wall of the ventricle and inserted on the dorsal cusp by one chord.

The third type of trabeculae, the moderator band, was found in all but eight hearts. This band increased from 2x0.5 mm at 66 days to 24x2 mm in the 280 day heart with many variations through the various aged hearts.

Left ventricle. The thickness of the left ventricle wall increases from 1 mm at 66 days to 23 mm at 280 days. The interior and exterior lengths of the ventricles also increased greatly, from 4 to 73 mm and 7-102 mm respectively.

The left ventricle has noticeably fewer trabeculae than does the right. Most of the original trabeculae are joined together by the invasion of muscle cells and of the fibrous connective covering. The wall of the 280 day heart is relatively smooth, with only the largest trabeculae being apparent. The two papillae are greatly enlarged and terminate in an average of 13 tough fibrous chordae tendineae (Fig. 11).

The chordae attach to the free edge of the valve cusp as in the 66 day heart, with a few attaching to the ventral surface of the cusp. Accessory tendineae as described for the 66 day heart are also present in the 280 day heart.

The semilunar valves. The valves have changed only by normal enlargement and elongation concomitant with the elongation of the respective arterial trunks. The position of the coronary artery openings in relation to the origin of the aortic semilunar cusps has undergone a change of position with age, by a relative anterior shift of the arterial orifice. The arterial openings of the 280 day heart lie approximately one-half the distance from the free edge of the cusp to its base. This position change results from elongation of the aorta, corresponding to the heart growth. The cusps of the pulmonary semilunars have undergone similar elongation. The distance from the origin of the aorta to the ductus arteriosus has increased from 2 mm at 66 days to 37 mm at 280 days (Fig. 12).

Changes in Size and Proportion

The weight of the hearts gradually increased from .22 grams at 66 days to 375 grams at 280 days (Fig. 13). There was some fluctuation of the heart weights below 104 days, but above 104 days there seemed to be little variation probably because a small variation in trimming and adherent water would not significantly affect the weight of the larger hearts.

Three hearts, 8-40, at 114 days, 8-54, at 96 days, and 8-56, at 80 days, were weighed after fixation with Bouin's fluid and again at the time of dissection with losses of 0.8, 0.7, and 0.115 grams respectively, mainly from the removal

of fixed blood from the interior of the hearts. All the other 64 hearts used in this study were flushed with water and fixed in a 10% formalin solution before weighing and dissection.

The length and thickness measurements of the heart also followed a gradual increase with thickness increasing less rapidly from 230 days until birth. Proportionate increase in length, width and thickness varied considerably. The heart at 65 days was longer, thinner, and more nearly round. The width increased more rapidly than either the thickness or the length, because of the individual increase of the right and left sides, with each side remaining nearly conical, but connected and somewhat restricted by the interventricular septum. The length: width: thickness ratio of the heart at 65 and 280 days was, respectively 10: 8: 6 and 148:91: 77, with measurements taken over the point of greatest length of the heart and greatest width of the ventricles (Fig. 14).

The Human Heart

The apex of the heart in the human lies to the left of the body midline (Fig. 17). This positioning of the heart enables us to observe the triangular shape of the heart from a ventral aspect. In contrast, the bovine heart parallels the midline, thus showing its triangular appearance from the ventral view.

The 60 day human heart shows the definite spiralling of the ventricles as seen in the 65 day bovine heart. The vessels along the interventricular septum are also evident. The position of the atria and the blood vessels of the atria and ventricles are positioned as in the bovine.

Aging causes a definite change in the external shape of the human heart, by 176 days the heart has taken a conical appearance with no definite division between the apices of the right and left ventricles. Also the coronary vessels overlying the interventricular septum are not easily identifiable (Fig. 16).

The aortic and pulmonary trunks and the ductus arteriosus are essentially in the same position in the human heart as they are in the bovine heart. But, the aortic trunk of the bovine divides into the brachiocephalic artery and the descending aorta while the aortic trunk of the human branches progressively into the innominate, left carotid, and left subclavian arteries before junction with the ductus arteriosus.

The right atrium is noticeably larger than the left and the opening of the inferior vena cava is very large and located on the dorsal surface of the atrium (Fig. 18). The pulmonary veins open on the anterior surface of the left atrium rather than antero-dorsal as in the bovine.

The right atrium of the human heart also contains five orifices, comparable with those of the bovine. The right atrium of the human contains a "right atrial valve" which arises on the interatrial surface and inserts just posterior to the postcaval openings (Fig. 19). This valve also constitutes the dorsal wall of the coronary sinus, thus only the foramen and the post-cava are located above the valve, which seems to direct the major flow of postcaval blood through the foramen ovale into the left atrium. The only major difference in the configuration of the atrium between the bovine and the human is that the main atrial chamber as well as the smaller surrounding chambers of the human possesses

many trabeculated muscles while that of the bovine is smooth at a comparable age. The position, origins and make-up of the atrio-ventricular valves of the human closely parallel those of the bovine.

The left atrium of the human also closely parallels that of the bovine in all respects except that the valve of the foramen ovale has no chordae tendineae. The main chamber of the atrium of both bovine and human have no trabeculated muscles, but the surrounding chambers contained many trabeculae in both.

There was also little difference between the ventricles of the bovine and the human. Each of the ventricles contained many trabeculated muscles and grooves between. The grooves in the human cut to a depth of one-half the wall thickness while those of the bovine cut only one-fourth of the wall thickness. The right ventricles of both contain three papillary muscles and their associated chordae tendineae attach to the tricuspid valves (Fig. 19). Likewise, the left ventricles of each contain two papillary muscles which give rise to chordae tendineae which attach to the bicuspid valve of the respective hearts.

Weights of the human heart (Table 2) make a logarithmic curve with a decrease in rate at older stages from 0.011 grams at 60 days to 4.2 grams at 176 days (Fig. 13).

Length and thickness of the human heart increase on a logarithmic scale (Fig. 15) similar to that of the bovine.

Table 2: Weight of heart of human fetuses and relation to body weight

| Embryo Number | Age: days | Sex | Weight, grams | | Heart weight: embryo weight |
|---------------|-----------|-----|---------------|-------|-----------------------------|
| | | | embryo | heart | |
| H-1 | 176 | F | 780 | 4.2 | 0.0053 |
| H-2 | 147 | F | 312 | 2.2 | 0.0070 |
| H-3 | 126 | M | 176 | 1.5 | 0.0085 |
| H-4 | 119 | F | 121.4 | 0.705 | 0.0057 |
| H-5 | 93 | F | 25.5 | 0.11 | 0.0043 |
| H-6 | 70 | F | 3.85 | 0.03 | 0.0042 |
| H-7 | 60 | F | 0.6 | 0.011 | 0.0018 |

Closure of the foramen ovale and the ductus arteriosus. Externally, hearts from calves one or two days after birth were not obviously different from those during the last few weeks of gestation. Internally, however, two changes can be detected. During fetal life, the valve of the foramen ovale is opened at each atrial systole by rush of blood from the right atrium through the foramen ovale. After birth, the pulmonary circulation increases rapidly, pouring blood into the left atrium, thus reducing the pressure differential between the two atria (Lind, et. al., 1964). At 24 hours post partum, the valve of the foramen ovale had begun to fuse with the septum progressively from the semicircular base of the valve toward the foramen. Fusion had progressed a little more by 48 hours, but the valve was yet functionally open. Some time within the first month of postnatal life, fusion of the valve with the septum is complete.

Closure of the ductus arteriosus apparently begins with the ending of placental circulation. At 24 hours after birth, the entire length of the ductus was noticeably smaller, and the lumen was becoming stellate, but was patent. By 48 hours after birth, closure had progressed, apparently by constriction, until the lumen was greatly narrowed near the middle of the ductus, but was yet def-

initely open. It was difficult to pass a probe through the center of the ductus indicating that the closure of the ductus begins at the center and moves both directions. Functional closure in the human occurs within a few days after birth, but anatomical closure does not occur for a few weeks (Lind, et. al., 1964). The actual anatomical closure of the ductus in the bovine is unknown.

CONCLUSION

The bovine and human hearts are essentially complete by 66 days and development continues only in increased size and weight.

The heart changes from a broad triangle to an elongate triangle by 280 days. The right atrium changes from globular to trapezoidal and the left to triangular by 280 days and the ventricles become more elongate triangular. The precava shifts anteriorly and the anterio-medial right pulmonary vein comes to open directly next to the interatrial septum. The only change in the arterial trunks is a proportional enlargement due to growth.

The foramen ovale shifts to a postero-dorsal position in close proximity to the orifice of the postcava and increases in size from 0.3 mm to 15 mm. The trabeculated musculature of the atrium increases and was present in all chambers of the atrium except over the interatrial septum. The only changes noted in the left atrium was the extreme enlargement of the valve of the foramen ovale, the shift of entrances of the pulmonary veins and the increased muscularization of the trabeculae in all but the main chamber of the atrium. The atrio-ventricular valves change only in size and in amount of fibrous tissue.

The only change in the right ventricle was by proportionate growth. The chordae progressively changed from muscular to fibrous and the moderator band, observed in all but eight hearts examined, increased in size and coursed diagonally across the cavity of the right ventricle. There was little change, except for normal growth, noted in the left ventricle.

The shift in position of the caval and pulmonary veins compared closely to that of the bovine. The right atrium formed a "right atrial valve", directs blood into the foramen ovale, and becomes trabeculated with increasing age.

A comparison of heart growth of the bovine to human respectively: 70 days, 0.305:0.03 gm.; 180 days, 98.7:4.2 gm.; and term, 374:15 gm.

ACKNOWLEDGEMENTS

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APPENDIX

EXPLANATION OF FIGURES

- 1: Dorsal aspect of a 65 day bovine heart
- 2: Ventral aspect of a 65 day bovine heart.
- 3: Interior of right ventricle and atrium, 65 day. Ventral wall of ventricle was cut both medially and laterally and hinged up at the atrio-ventricular junction.
- 4: Internal of left ventricle and atrium, 65 day. Ventricle was cut only along medial border and opened.

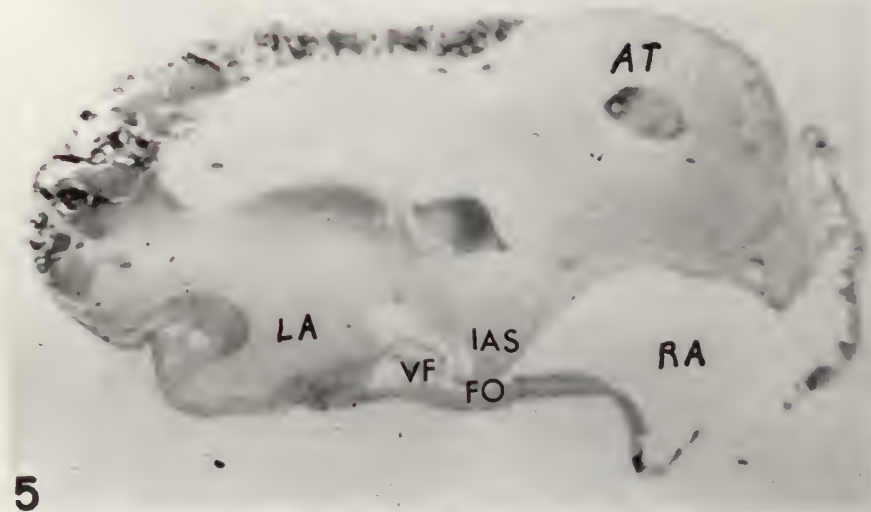
The guide letters used for identification of structures in all figures are:

A-atrium, AC-anterior caval vein, AP-apex, AT-aortic trunk, AW-atrial wall, CA-coronary artery, CS-coronary sinus opening, CT-chordae tendineae, DA-ductus arteriosus, FO-foramen ovale, IAS-inter atrial septum, IVS-inter ventricular septum, L-lung, LA-left atrium, LV-left ventricle, MB-moderator band, MVC-medial valve cusp, PC-postcava, PM-papillary muscle, PT-pulmonary trunk, PV-pulmonary veins, RA-right atrium, RAV-right atrial valve, RV-right ventricle, SV-semilunar valve, TM-trabeculated muscle, V-ventricle, VC-valve cusps, VF-valve of foramen



EXPLANATION OF FIGURES

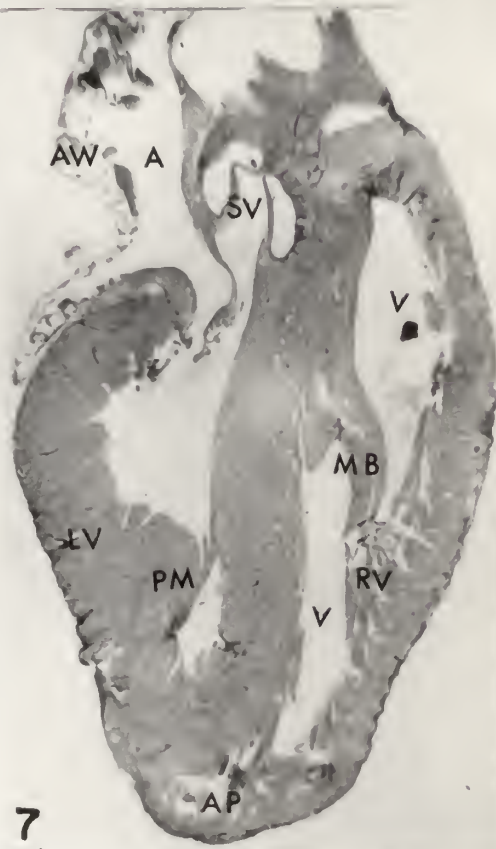
- 5: Transverse section through the atria of a 73 day bovine fetus. The valves of the foramen show, in section, as a coarse net of valve and chordae.
- 6: Longitudinal section of a heart from a 75 day bovine fetus. The inter-ventricular septum is complete, mitral valves, and semilunar valves fully functional, and off the aortic trunk, immediately above the medial cusp of the semilunar valve, the orifice of the carotid artery is obvious.
- 7: Another section of the same heart as shown in Fig. 6, a little more dorsally, showing the full length and width of the moderator band across the right ventricle.



5



6



7

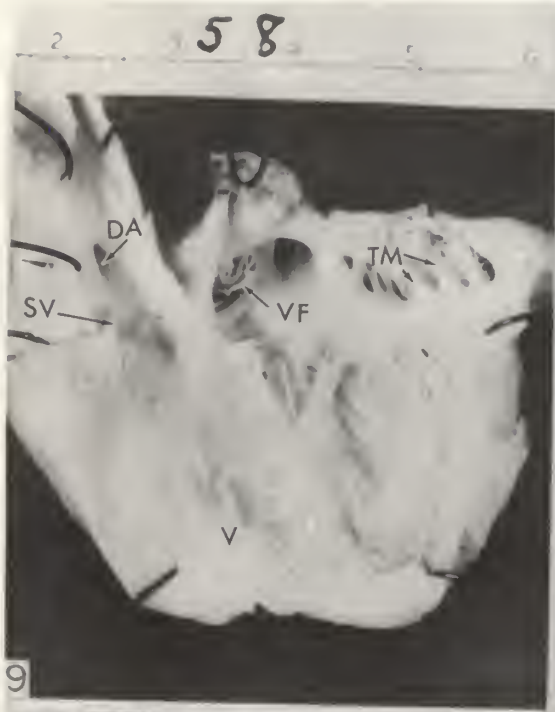
EXPLANATION OF FIGURES

8: Composit of bovine hearts; A-65 days, B-90 days, C-132 days, D-195 days. These hearts were all arranged on one background and photographed together, so relative sizes are absolute. Centimeter rule at bottom gives actual size.



EXPLANATION OF FIGURES

- 9: Internal aspect of 132 day, left atrium and ventricle of bovine.
- 10: Dorsal aspect of 280 day bovine. The caval orifices are separated and surface fat has begun accumulating.
- 11: Internal aspect of left atrium and ventricle of 280 day bovine. Chordae tendineae have become almost completely fibrous. The valve of the foramen ovale has begun its rapid growth.
- 12: Internal aspect of 195 day bovine, left atrium and ventricle. Some trabeculated muscles in ventricle hav become separated except at their ends and may be considered as secondary "moderator bands".



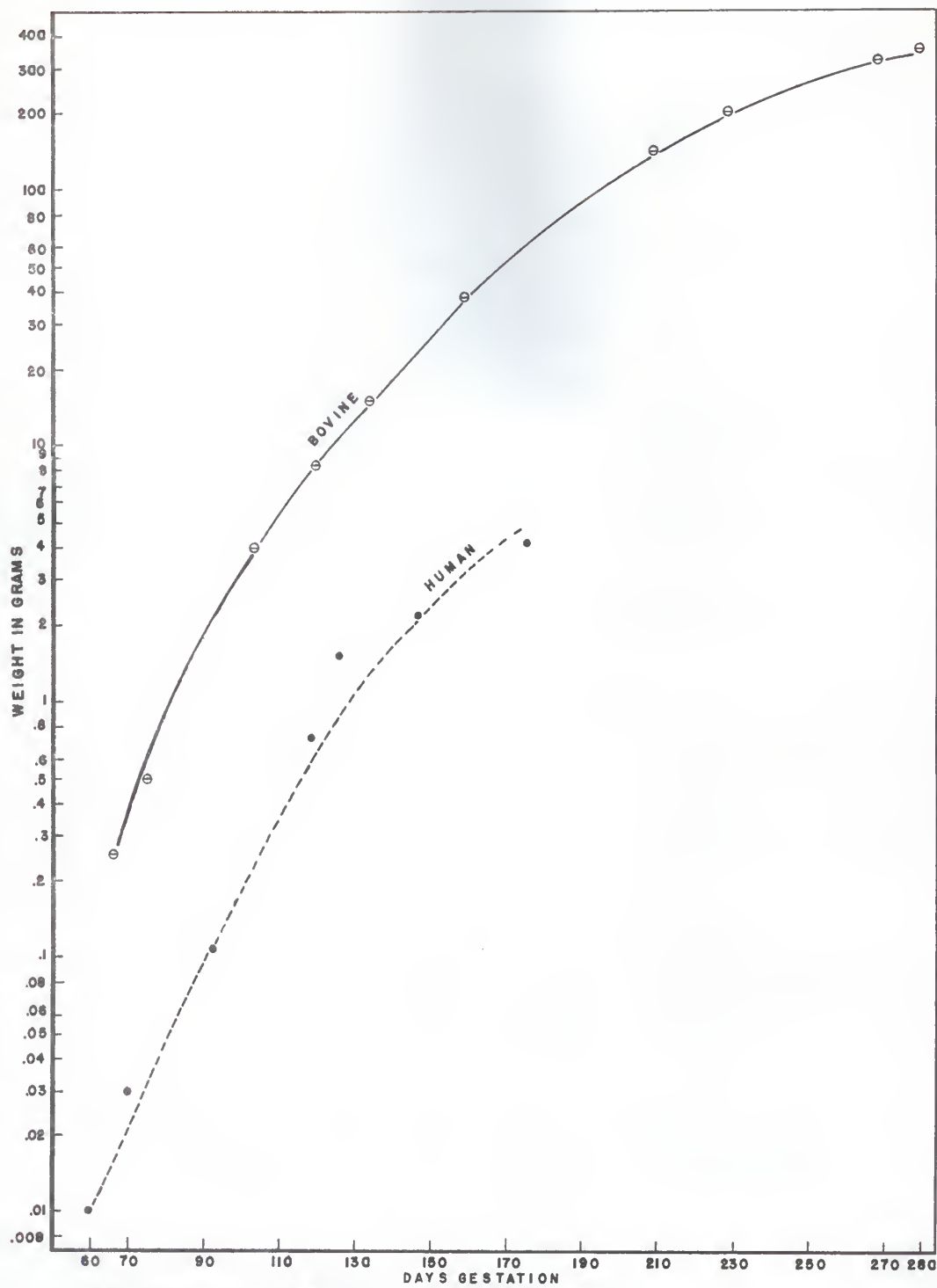


Fig. 13. Human and bovine heart growth by weight.

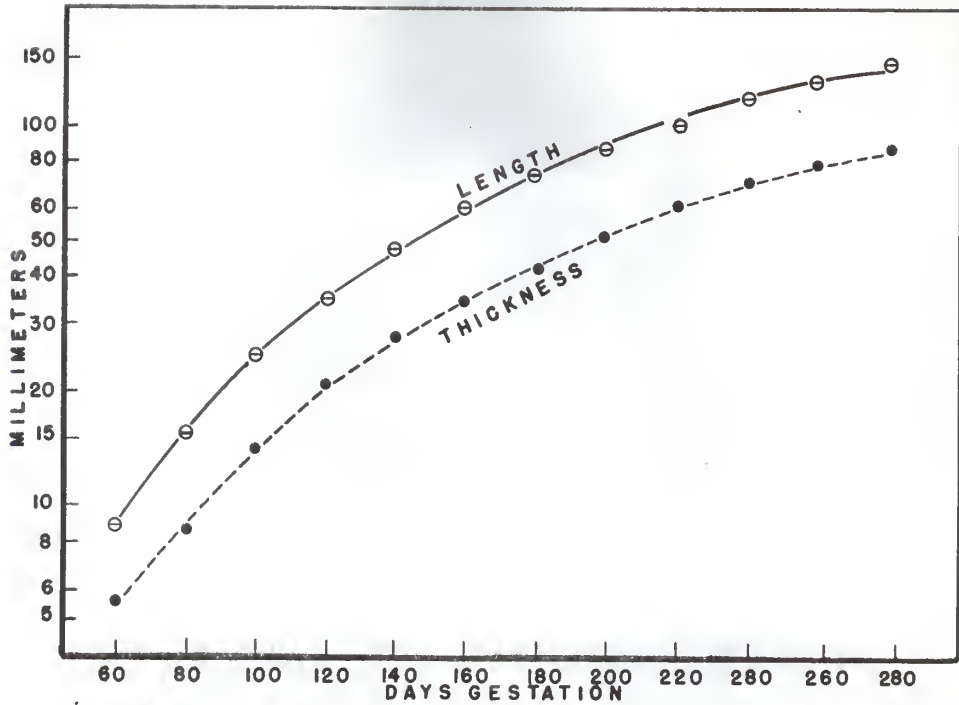


Fig. 14 Bovine heart growth from 60 to 280 days. Length and thickness.

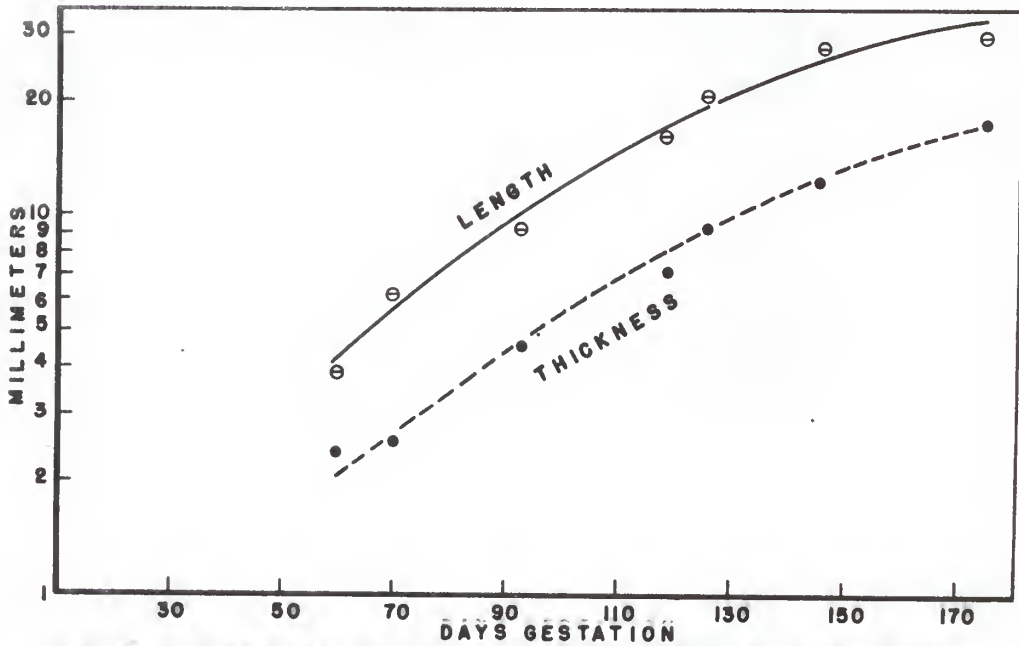
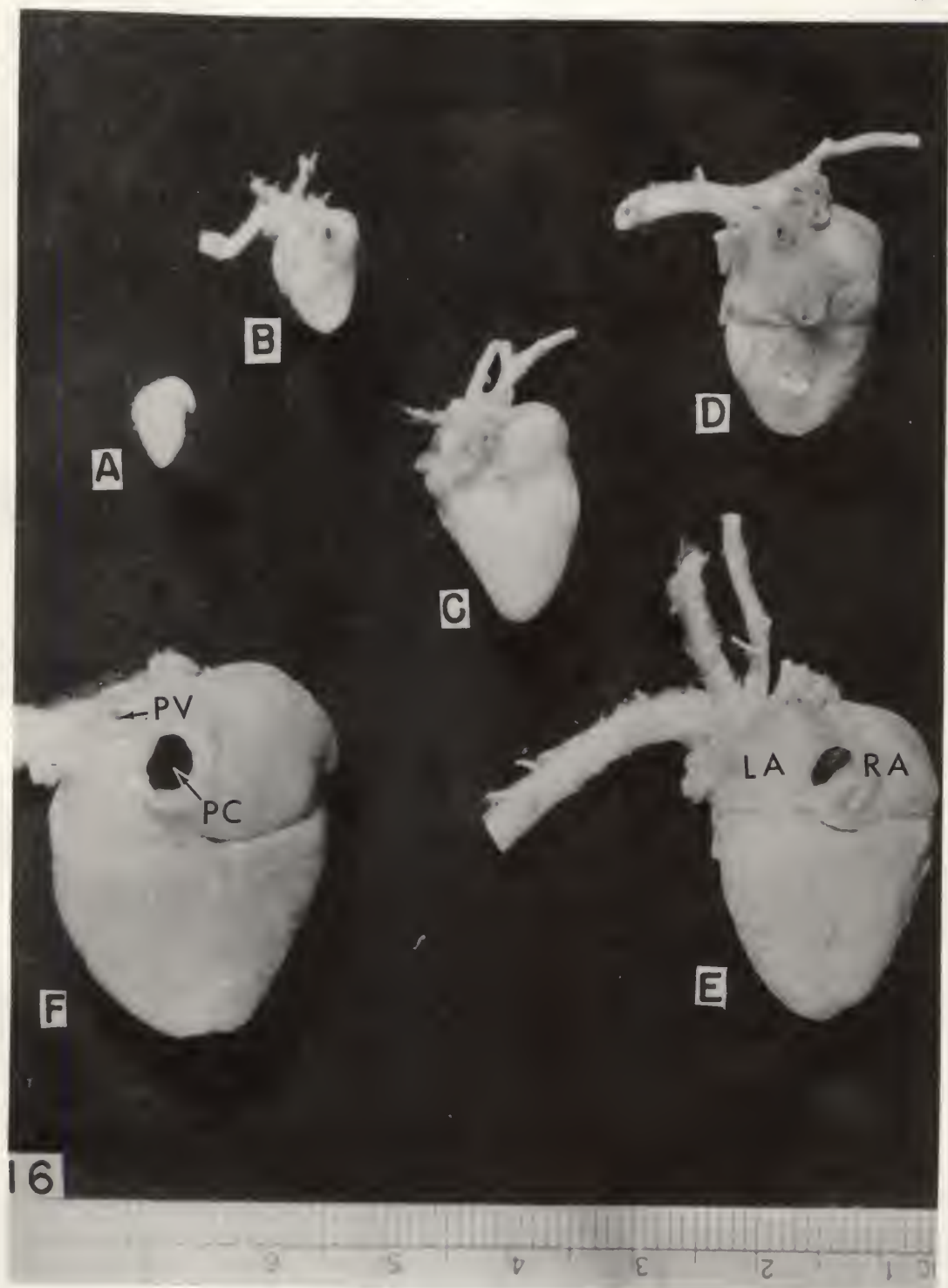


Fig. 15 Human heart growth from 60 to 176 days. Length and thickness.

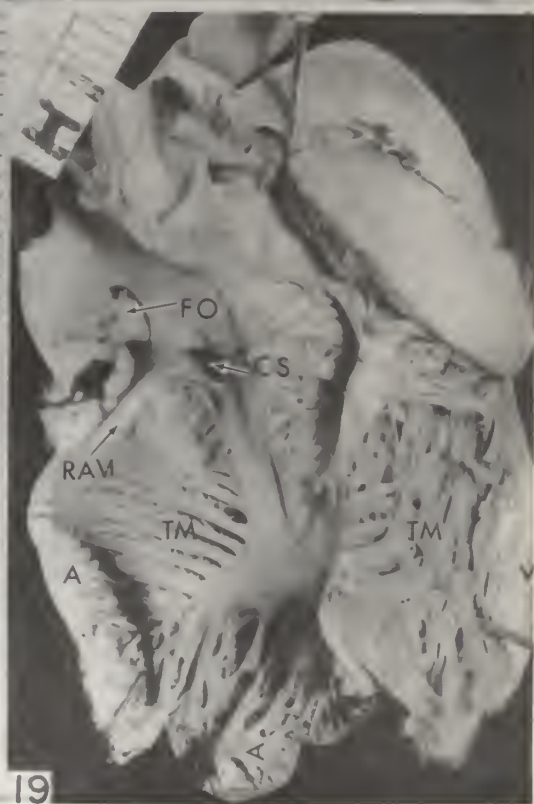
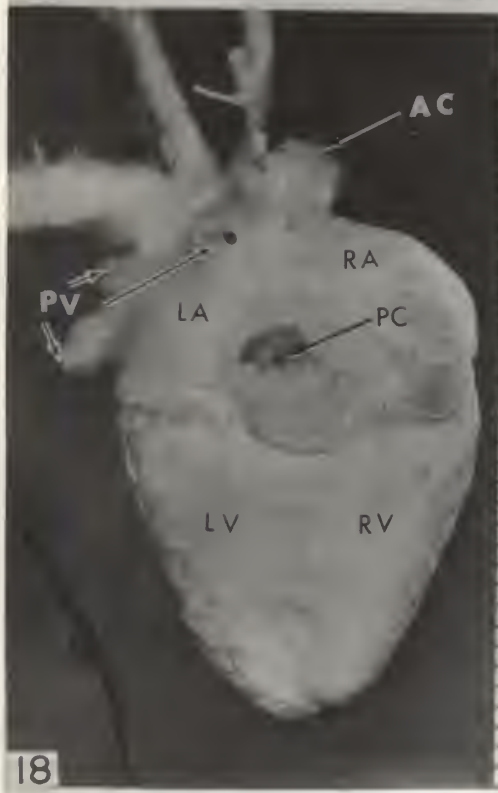
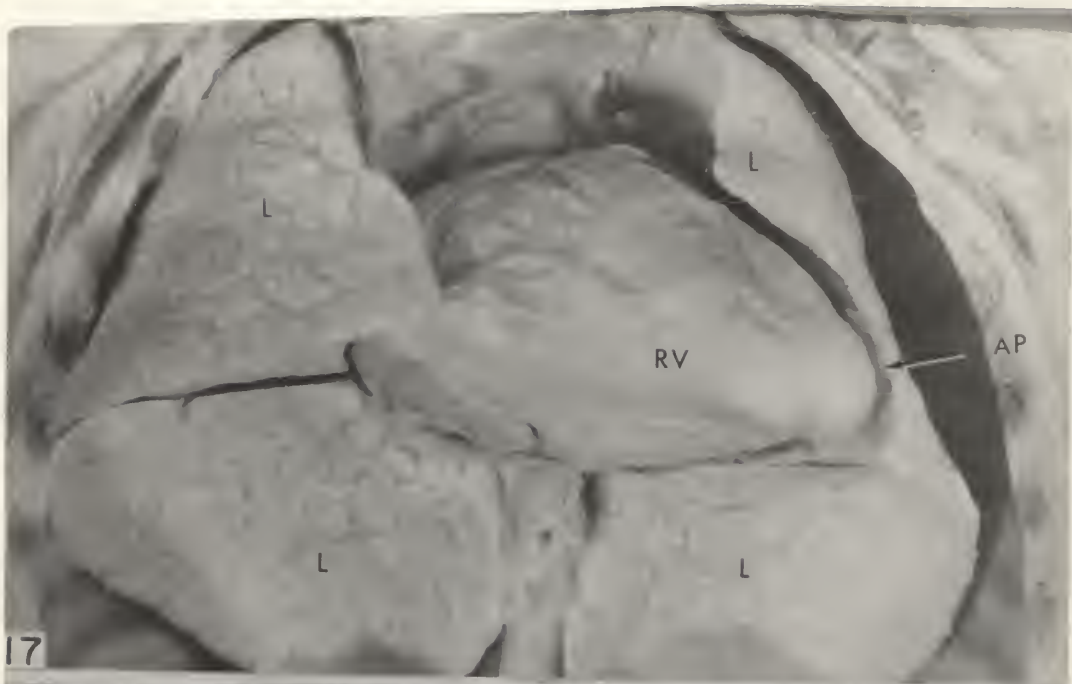
EXPLANATION OF FIGURES

16: Composit of Human hearts ages; A-70 days, B-93 days, C-119 days, D-126 days, E-146 days, F-176 days. Dorsal aspect. These hearts, as their counterparts in Fig. 8, were all photographed together.



EXPLANATION OF FIGURES

- 17: Thoracic dissection of a 146 day human showing the heart in normal position with apex oriented to left side.
- 18: Dorsal aspect of 146 day human. Anterior and posterior caval orifices are widely separated. Both ventricles extend essentially to the apex.
- 19: Internal aspect of right atrium and ventricle of 176 day human heart. Trabeculated muscles in the ventricle are highly differentiated, anastomosed, and are not uniformly oriented. In the atrium, trabeculated muscles are parallel, particularly around the main lumen.



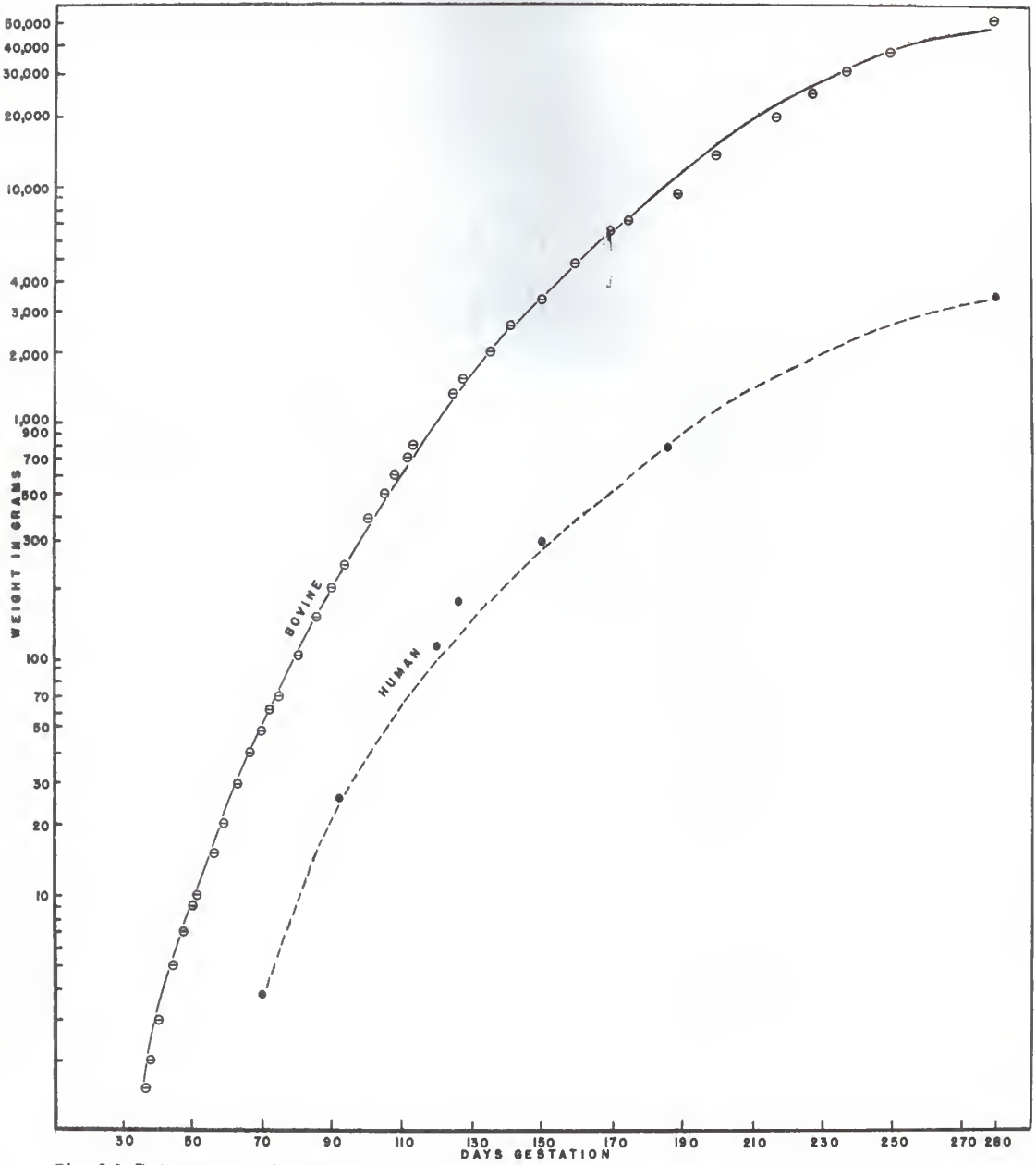


Fig. 20 Total growth of human and bovine fetuses by weight.

GROSS DIFFERENTIATION OF THE HEART
IN THE BOVINE AND HUMAN

by

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AN ABSTRACT OF A MASTER'S THESIS

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ABSTRACT

Hearts from 67 bovine fetuses 64 days gestation to 2 days after birth and from seven human fetuses 60 to 180 days were examined for anatomical and size changes. The hearts were studied in situ, then excised, weighed, measured, and dissected for detection of internal changes. A representative series was photographed for permanent record. Graphs were constructed to show growth rates.

At 60 days in the human and 64 days in the bovine, all four chambers were formed. The shape changed gradually by broadening of the ventricles and relatively greater increase in length of the ventricle. Spiral configuration of the interventricular septum at 64 days was lost by 150 days. External appearance of trabeculated muscles in the atria disappeared by midgestation as the atrial walls thickened. Pre- and postcavae, separated only by the sinuaricular node at 64 days, gradually separated, and by birth they had reached their definite positions. The pulmonary veins originally all joined the left atrium in a cluster; one right pulmonary vein shifted far medially, directly against the interatrial septum. The interventricular septum was complete at 64 days, papillary muscles established, and all valves developed and functioning. Trabeculae carneae were distinct, with deep grooves between which gradually became less distinct by invasion of muscle and connective tissue.

A moderator band was found across the right ventricle in all but eight bovine heart and in all seven human hearts. Numerous fibrous "moderator" bands were found in all left ventricles. Two papillary muscles with 5 to 7 chordae tendineae

each were present in all left ventricles; three in most, four in one right ventricle, with 5 to 7 chordae on each. Valves became progressively more fibrous.

Atria were globular at first, gradually spreading and developing angular borders. Trabeculae were present at 65 days only in the auricles and other secondary chambers with little muscle between, but by birth, the wall between trabeculae is approximately the same thickness as the trabeculae.

The interatrial foramen shifts from a medial position in the interatrial wall to a postero-ventral position directly opposite the postcava. The valve of the foramen is fused to the septum around all but one-eighth of the original foramen. The valve increases disproportionately, producing a surplus of tissue which begins degeneration by 280 days. The loose edge of the valve is connected to the interatrial septum by 2 to 5 chordae tendineae.

The weight of the heart increased from 0.22 gm. at 65 days to 374 gm. at 280 days, at a decreasing logarithmic rate.

The 65 day heart was 10 mm long, 8 mm wide and 6 mm thick and was oval in all planes but by 280 days, it had become an elongated triangle 148:91:77 mm. The width increased more rapidly than the length and thickness.

In the human heart, the pulmonary veins open on the anterior surface of the left atrium as opposed to the antero-dorsal surface in the bovine. The main right atrial chamber contains many trabeculated muscles at 70 days. The valve of the foramen ovale has no chordae tendineae. The ventricles of the human heart showed no basic difference from those of the bovine at any time. Weights of human hearts gradually increase from 0.011 grams at 60 days to 4.2 grams at 176 days on a decreasing logarithmic curve.