Ceylon J. Med. Sci. (D) Vol. XIV No. 2, (December 1965)

The Development of the Specialized Musculature of the Human Heart[1]

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Although the presence of specialized musculature in the heart of Man and other mammals is generally accepted by most investigators, the precise ontogenetic origin of the specialized tissue is still disputed. For instance Field (1951), investigating sheep embryos, suggested that the specialized appearance of the musculature in the atrioventricular bundle is due to its retention of embryonic characters whereas Muir (1954), investigating the same species came to the opposite conclusion that the atrioventricular bundle is a new formation resulting from specific differentiation of part of the embryonic myocardium. In view of this controversy, a review of the problem together with fresh information is desirable.

REVIEW OF LITERATURE

The sinus node[2]

When Keith & Flack (1907) found the sinus node at the base of the right precaval vein in several mammalian species, they suggested, on the basis of comparative studies, that it is a phylogenetic remnant of specialized junctional musculature more widely distributed at the sinu-atrial ring in lower vertebrates. Similarly, they regarded the atrioventricular connecting system as a phylogenetic remnant of specialized tissue at the atrioventricular junction. On the other hand, Davies & Francis (1946) were unable to find histological specialization in any part of the heart in poikilothermal animals (fish, amphibia and reptiles) and concluded that specialized muscle has been evolved at certain sites in the hearts of homoiothermal animals (birds and mammals) for the initiation and conduction of the cardiac impulse. These conclusions by Davies and Francis are now more widely accepted than the earlier concepts of Keith and Flack.

The earliest views on the ontogenesis of the sinus node were merely extensions of the phylogenetic ideas of Keith & Flack, in that they presumed that the node must be a remnant of the embryonic sinu-atrial region. However, Stiénon (1926), who followed cardiac development in Man from the 6.4 mm. stage and in the rabbit from the 6.5 mm. stage, observed that the sinus node appeared only after the 22.4 mm. stage, by which time the cardiac nerves had reached the nodal site. On the basis of these observations, he suggested that the node is a new formation, differentiating to serve as an intermediary between the neural elements and the myocardium. A similar view has been expressed by Shaner (1929, 1930), who studied calf embryos.

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[1] Based on part of a thesis entitled ' The development of the nerve supply to the human heart ', which was accepted for the Ph.D. degree of the University of Cambridge in 1964.

[2] This term is preferred to the terms ' sinu-atrial node ' and ' sinu-auricular node ' because it is simpler and, for reasons outlined later in this communication, less controversial.

Many other authors, including Sanabria (1936), Walls (1947) and Duckworth (1952), all of whom studied human embryos, have agreed with Stiénon that the sinus node is a new formation and not a remnant of tissues more widely distributed in the embryonic heart. However, they believed that its differentiation precedes the arrival of neural elements at the nodal site but this opinion is hardly surprising because they had used material in which nerves are stained by non-specific methods.

The precise embryological site of the sinus node is still disputed. Stiénon (1926) assigned the node to the junction of the right precaval vein and the right sinus horn, rather than to the junction of the right sinus horn and the right atrium where Keith & Flack (1907) and Mackenzie (1913) supposed it to lie. Shaner (1929) and Muir (1955), investigating the calf and the rat respectively, have suggested that the node migrates from the right cavo-sinus junction to its definitive position at the right sinu-atrial junction. Patten (1956) has also supported Stiénon's view on the site of origin of the node but considered that the true cavo-sinus position of the node becomes masked by absorption of the right sinus horn into the right atrium rather than by active shift of the node. On the other hand, Rawlinson (1931) was convinced that the node in the calf can be assigned to the sinu-atrial junction from the start, an interpretation which is supported by the observations of Walls (1947) and Duckworth (1952) in Man. James (1961), however, expressed his unwillingness to enter into the controversy regarding the cavo-sinus or sinu-atrial status of the node and suggested that the node be regarded as part of the sinus venosus rather than of either junctional region.

The atrioventricular node

In their scheme of specialized junctional musculature, Keith & Flack (1907) assigned the nodal mass, which Tawara (1906) had found at the atrial end of the atrioventricular bundle, to the atrioventricular junctional region ; on the other hand, Koch (1909) and Mackenzie (1913), who laid more emphasis on the relationship of Tawara's node to the coronary sinus, suggested that it is a counterpart, on the left side, of the sinus node. The latter investigators envisaged that a node is formed at the junction of each sinus horn with the atrium but that, as the left horn is shifted caudally and ventrally, the corresponding node is carried near the atrioventricular region. Patten (1956) also supported the concept of bilateral and symmetrical sinus pacemakers but considered that they are formed at the cavo-sinus junction on each side. He suggested that Tawara's node reaches its definitive position as a result of complete absorption of the left sinus horn into the right atrium, an absorption which is denied, however, by most other embryologists.

In fact, most accounts of the ontogenesis of Tawara's node in Man (Wahlin, 1935 ; Sanabria, 1936 ; Walls, 1947 ; Duckworth, 1952) and in other mammals (Shaner, 1929 ; Calcagno, 1941 b ; Field, 1951 ; Muir, 1954) describe its formation in the dorsal wall of the atrioventricular canal. If the node does appear initially in the dorsal wall of the atrioventricular canal, i. e. symmetrically between the two atria; as the majority of embryologists have indicated, one must elucidate how it comes to lie in the right atrial wall, near the coronary sinus orifice.

The atrioventricular connecting system

His, Jr. (1893), in his original description of the atrioventricular bundle implied that it is a remnant of the embryonic atrioventricular canal wall although he did not actually observe the early stages in the development of the bundle. On the other hand, Shaner (1929), Walls (1947) and Duckworth (1952) came to the conclusion that the bundle is an outgrowth of the nodal anlage in the dorsal wall of the atrioventricular canal.

Mall, (1912), in an investigation of a series of human embryos, observed that the presumptive site of the atrioventricular bundle can be identified in the dorsal wall of the atrioventricular canal at the 8 mm. stage, before the invasion by fibrous tissue, and that the bundle primordium is subsequently spared from disruption by the fibrous tissue. Thus, while stressing that the bundle is a derivative of the wall of the original embryonic atrioventricular canal, he advanced the idea that " early in development it shows changes in structure which differentiate it from the rest of the heart muscle ". Many other investigators have supported Mall's hypothesis of development by differentiation *in situ* but there has been little agreement on the details of the process.

Wahlin (1935), suggested that the differentiation of the atrioventricular node and bundle, in that order, is induced by the growth of nerves into the dorsal wall of the atrioventricular canal. On the other hand, Sanabria (1936) and Muir (1954) were convinced that the bundle differentiates before the node ; this sequence of events is puzzling because both these authors found that the bundle itself differentiates from its atrial end towards the ventricles. Calcagno (1941 a & b) also observed, in the calf, that the atrioventricular node develops after the bundle but he believed that the two structures arise quite independently and that they blend together at a later stage of development.

Field (1951) and Patten (1956) adopted a different line of reasoning in interpreting the development of the connecting system. In their opinion the eventual specialized appearance of the conducting tissue is due to its retention of embryonic features while the surrounding general myocardium differentiates faster. To support this hypothesis Patten demonstrated that all parts of the embryonic chick heart are capable of conducting the cardiac impulse in a manner similar to that operative in the postnatal atrioventricular bundle ; he postulated that the embryonic myocardium is progressively restricted by newly developed musculature and that it thus assumes the definitive form and distribution of the nodal and connecting systems. In this connection, Robb & Petri (1961) have claimed that they can identify two different populations of muscle in the developing chick heart ; an embryonic ' trabeculum ', which becomes the atrioventricular connecting system, and a secondary ' compact ' stratum which becomes the general myocardium. Since there is no reason to believe that the development of the connecting system in Man differs fundamentally from development in the chick, it is of interest to determine whether the myocardium in young human embryos exhibits the features described by Robb and Petri.

MATERIAL AND METHODS

Serial sections through the hearts of ninety-one human embryos and foetuses, ranging from 4 mm. to 310 mm. C. R. length, and in two newborn infants were examined. These specimens are included in the collection at the Department of Anatomy, University of Cambridge. Completely serial sections of all the specimens less than 60 mm. C. R. length were available but, because of their large size, the hearts of the advanced foetuses and of the infants were dissected out and regularly interrupted serial sections were prepared. Most of these specimens were sectioned in the transverse plane but several others were sectioned either in the coronal plane or in the sagittal plane; it must be appreciated, however, that complete series of true transverse, coronal or sagittal sections are highly improbable owing to the curvatures of the embyonic axis.

The material was stained by a large variety of histological methods, including Bodian's silver impregnation using Roques's silver proteinate, De Castro's silver impregnation, modified Masson's trichrome, modified Goldner's trichrome, P. A. S., cresyl violet and haematoxylin and eosin.

OBSERVATIONS

Embryos measuring less than 10 mm. C. R. length

The myocardium is uniformly made up of spindle-shaped cells, within which no striations can be identified at this stage. In the youngest embryos there is no evidence of the existence of two different populations of muscle cells in the general myocardium.

The junction between the sinus venosus and the right atrium (i.e. the sinu-atrial junction) is delineated by the mural attachments of the prominent right and left venous valves and, at this stage of development, it can be clearly distinguished from both cavo-sinus junctions i. e. the junctions between the sinus horns and the corresponding common cardinal veins; however, because the right sinus horn is already wider and shorter than its counterpart on the left side, it is easy to understand why distinction between the right cavo-sinus junction and the sinu-atrial junction becomes difficult later in development.

The muscular wall of the sinus venosus, which comprises the sinus bay (i. e. the region between the two venous valves) as well as the two sinus horns, has a characteristic whorled appearance that is uniform throughout its extent. There are no collections of distinctive tissue in the wall of the sinus venosus ; nor is there distinctive tissue at the sinu-atrial or cavo-sinus junctions.

The lower part of the sinus bay is divided into two parts by a thick ridge, the sinus septum, which lies in the coronal plane. The upper border of the sinus septum is covered with endocardium and it lies between the right vitelline vein posteriorly and the left sinus horn anteriorly, while its base is continuous with the mesodermal tissue in the venous mesocardium and the septum transversum. At its left end the septum blends just above the dorsal atrioventricular cushion with the dorsal limb of the interatrial septum primum and with the caudal end of the left venous valve, while its right margin is directed towards the base of the right venous valve.

Although there is already some connective tissue in the atrioventricular sulcus, the continuity between the atrial and ventricular musculatures is complete. The muscle cells in the atrioventricular canal wall are arranged circumferentially except where the dorsal wall of the canal is continuous with the ventricular myocardium (fig. 1). Here the inner muscular layers are arranged parallel to the longitudinal axis of the canal. This longitudinal fasciculus of cells, which is aligned with the muscle fibres situated at the free margin of the crescent-shaped interventricular septum, is more compactly arranged than the surrounding myocardium and thus appears denser and darker than the latter at this stage. Mitotic figures can be observed in some of the cells in the fasciculus (fig. 2) but they do not occur more frequently than in the general myocardium. The fasciculus can be identified at the 7.5 mm. stage, before any nerves have reached the heart.

Embryos measuring 10 mm. to 16 mm. C. R. length

Although a large portion of the right horn of the sinus venosus is now intussuscepted into the right atrial cavity, the prominent venous valves clearly demarcate the sinus wall from the atrial wall. It is thus easy, even at this stage, to distinguish the sinu-atrial junction from the right cavo-sinus junction (fig. 3). At neither of these sites is there a collection of muscle cells differing from the characteristic sinus musculature in arrangement or in cytological features. However, after the 11 mm. stage, nerve fibres ramify at the mural attachments of the upper part of the right venous valve and of the septum spurium ; these nerve fibres are branches of the right sinus nerve (see Navaratnam, 1965). The general musculature of the heart consists of spindle-shaped cells in many of which cross-striated fibrils can now be recognized.

The muscular continuity between the atria and ventricles is breached in several places by fibrous strands bridging the atrioventricular cushions with the subepicardial tissue (fig. 4). However, some of the previous continuity is maintained in the form of muscular fascicles. Many of these fascicles are tenuous and their positions vary from specimen to specimen but one connecting fascicle is found at the same site in every embryo at this stage. This constant muscular fascicle, which is the atrioventricular bundle, extends from the lower part of the dorsal atrial wall to the atrioventricular septum by passing on the dorsal aspect of the right atrioventricular opening (fig. 5). The position of the bundle is identical with that of compact fascicle of longitudinally arranged cells seen in younger embryos. At its atrial end it now consists of loosely and irregularly arranged muscle cells (fig. 6) among which several nerve fibres are dispersed. This well innervated, loosely arranged region is the primordium of the atrioventricular node ; the nerves ramifying in it are derived from both sides of the body and they reach the nodal site by running along the pulmonary veins. There are no nerve fibres in the connecting bundle apart from those at its atrial end, in the nodal primordium. At its ventricular end, the connecting bundle extends along the free upper border of the muscular interventricular septum and merges with the myocardium in the septum (the interventricular foramen is still patent although it is much reduced by encroachment by the atrioventricular and bulbar cushions). The bundle stands out from the septal musculature owing to its compact arrangement (fig. 7) ; some of its cells contain mitotic figures but their frequency is similar to that in the general myocardium.

Embryos measuring 17 mm. to 29 mm. C. R. length

The right common cardinal vein can now be recognized as part of the superior vena cava. This vessel opens almost directly into the sinus bay of the right atrium but it is still possible to distinguish the cavo-sinus junction from the sinu-atrial junction. Near the latter junction, at the mural attachments of the septum spurium and adjacent part of the right venous valve, there is a distinct collection of cells (fig. 8), which is undoubtedly the anlage of the sinus node. The nodal cells are stained more palely than the adjacent atrial and sinus muscle fibres and are also more loosely and irregularly arranged. Although numerous small blood vessels ramify within the node, there is not at this stage a single prominent vessel. The nodal mass, which becomes recognizable at about the 20 mm. stage, extends caudally about halfway along the mural attachment of the right venous valve ; it certainly does not extend to the atrioventricular region. Several nerve fibres ramify within the node, on the surface of which there are small clumps of ganglion nerve cells.

During this stage of development, the left venous valve is reduced in extent by the infolding of the atrial wall in the intersepto-valvular space. This infolding is an early stage in the formation of the septum secundum ; it first appears in the cranial wall of the atrium but it subsequently extends dorsally, towards the intersepto-valvular space, and ventrally towards the atrioventricular region and the sinus septum.

The ventral extension of the septum secundum moulds the conjoined sinus septum and septum primum towards the atrial cavity. As a result the adjacent atrioventricular node is carried atrialward so as to lie between the interatrial septum and the atrioventricular cushion mass rather than in its original position behind the dorsal cushion. Another result of the moulding in this region is the approximation and subsequent fusion of the connective tissue in the sinus septum with the atrioventricular cushion mass i. e. with the fibrous trigone ; this connective tissue condenses to form a tendon-like structure (see fig. 9), the tendon of Todaro, which arches over the atrioventricular node.

The cells in the atrioventricular node are lightly stained owing to the paucity of cross-striated myofibrillae and they are arranged in a loose network similar to the arrangement in the sinus node. On its right side, the atrioventricular node is continuous with the more compact atrioventricular bundle, which consists of cells similar to the nodal cells. The bundle passes between the subepicardial fibrous tissue and the atrioventricular cushion mass near the base of the septal cusp of the right atrioventricular valve. It then courses along the junction of the muscular and fibrous parts of the interventricular septum (the interventricular foramen is usually completely closed during the 17-20 mm. stage and it is noteworthy that the newly formed *pars membranacea septi* is attached to the fibrous trigone in a plane distinctly to the right side of the attachment of the interatrial septum to the trigone). After a short course the bundle divides into two branches which resemble the common bundle in structure. These two branches are the left and the right bundle branches, which merge with the muscular trabeculae in the left ventricle and right ventricle respectively ; at this stage the left bundle branch is more conspicuous than its fellow.

Foetuses measuring 30 mm. to 60 mm. C. R. length

During the 30-40 mm. stage a segment of the left common cardinal vein, near its entry into the left sinus horn disappears. The upper part of the left sinus horn becomes attenuated, forming the oblique atrial vein, whereas its lower part receives the cardiac veins and enlarges to become the coronary sinus. There are no collections of specialized muscle fibres in the wall of either the left common cardinal vein or the left sinus horn.

The sinus node is a comma-shaped structure, the body of which lies in front of the superior caval inlet (it is no longer possible to distinguish the sinu-atrial junction from the cavo-sinus junction) ; the tail lies at the mural attachment of the upper part of the right venous valve i.e. at the upper part of the crista terminalis. As the septum secundum develops, the cranial end of the node is pulled into the interatrial sulcus. The node is formed of slender spindle-shaped muscle fibres with few myofibrillae. These fibres, each of which has approximately half the width of a muscle fibre in the general atrial myocardium, are grouped irregularly round a distinct nodal artery in contrast with the regular palisade disposition of the atrial myocardium. The sinus nodal artery usually arises from the right coronary artery. It courses backwards in the superior interatrial sulcus and, turning in front of the superior caval inlet, it runs axially through the body and tail of the node (figs. 10 & 11). In no specimen is there an extracoronary blood supply to the node.

The structure and arrangement of the atrioventricular node is very similar to that of the sinus node. Like the latter, the atrioventricular node is supplied by a distinct artery. This vessel usually springs from the terminal part of the right coronary artery, before the latter turns into the inferior interventricular sulcus, but occasionally it arises from the circumflex branch of the left coronary artery.

The P. A. S.-stained material does not support the view that there is more glycogen in the nodal and connecting systems than in the general myocardium. Indeed, it appears that the specialized musculature stains less intensely with P. A. S. than does the general myocardium.

Differentiation of the branches of the atrioventricular bundle has extended further into the ventricles than at previous stages of development. The left bundle branch is a flat sheet which spreads on the left side of the interventricular septum and merges with undifferentiated myocardium about midway between the base and apex of the left ventricle. The right bundle branch is a more compact fascicle, which passes deep to the ventral bulbar cushion and surfaces at a point distal to the cushion. The cellular elements of the proximal parts of the bundle branches are similar to those of the common bundle and of the atrioventricular node but in the distal parts, the cells are of approximately the same size as the general myocardial fibres and are stained similarly. Enlarged subendocardial cells, corresponding to the cells observed by Purkinje[3] in the sheep, are not present in either ventricle at this stage of development.

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[3] Purkinje's observation was first reported by his student Palicki (1839)

Apart from the atrioventricular bundle, connections between the atrial and ventricular musculatures are very few and, when present, they are irregular in position.

Foetuses exceeding 60 mm. C. R. length and newborn infants

Apart from an apparent decrease in size, relative to the size of the heart in general, there is little change in the form of the sinus node. During the late foetal period, the quantity of connective tissue in the interstices of the node increases but, even at full term, the node is not completely encapsulated. Hence, the peripheral nodal cells often lie in direct contact with the larger, more obviously striated fibres of the atrial myocardium.

The atrioventricular node has upto this stage lain symmetrically between the two atria, between the interatrial septum and the atrial surface of the fibrous trigone. Now, as part of the trigone becomes aligned with the interatrial and interventricular septa to become the *atrioventricular* septum intervening between the right atrium and the vestibular part of the left ventricle, the node is shifted gradually towards the right atrium (fig. 12). Throughout this shift, the tendon of Todaro, which arches over the node, remains a reliable guide to the nodal position (fig. 13).

The musculature of the atrioventricular node passes in front of and above the coronary sinus orifice and comes into contact with the muscle fibres in the sinus and interatrial septa. It is through the sinus septum that nerve fibres reach the node and on the surface of the latter there are clumps of ganglion nerve cells. Some nerve fibres pass through the node into the adjacent part of the bundle but few, if any, continue into the ventricular part of the bundle.

As the contribution to the fibrous trigone by the subepicardial tissue increases, the bundle becomes buried more deeply within the trigone (see fig. 8). After piercing the trigone, the bundle is encased in a sheath of fibrous tissue, which generally prevents contact between the bundle elements and the septal myocardium ; occasional muscle strands, however, do pass through the sheath.

Where the bundle bifurcates, just beneath the aortic semilunar valve, each bundle branch carries an extension of the fibrous sheath. The left bundle branch is a broad flat sheet which ends about halfway down the left surface of the interventricular septum (fig. 14). In this region many of the subendocardial muscle cells related to the bundle branch are moderately enlarged and their cytoplasm is stained very poorly ; moreover, only irregular fragments of myofibrillae can be identified within them.

The right bundle branch inclines to the right and appears in the subendocardial tissue at a variable level on the right surface of the interventricular septum. However, it does not blend with the general myocardium here because its fibrous tissue sheath persists tills it reaches the base of the moderator band. Within the moderator band or at the base of the anterior papillary muscle, the sheath fades away and the bundle branch elements blend with the myocardium. Along the distal part of the right bundle branch there are present several swollen muscle fibres with poor cytoplasmic staining and fragmented myofibrillae, Mitotic figures occur in the cells of the common bundle and bundle branches but they occur in the same frequency as they occur elsewhere in the myocardium ; there is nothing to suggest that any part of the connecting system is a site of increased proliferative activity.

DISCUSSION

None of the specialized structures are present in the heart before the 7. 5 mm. stage (i. e. before the fifth week of gestation). Thus it is unlikely that differentiation of the specialized tissues can be responsible for the initiation of the heart beat in the embryo, a phenomenon which occurs at about the third week of gestation in Man (Pflüger, 1877). It is probable that, as Patten (1956) has claimed, all parts of the undifferentiated embryonic myocardium are capable of initiating and conducting the cardiac impulse.[4] Nonetheless, in the present study there is no evidence to support Patten's hypothesis that the embryonic myocardium is retained as the specialized musculature of the definitive heart while the general myocardium is secondarily added. Indeed, the present observations on development from the fifth week of gestation till full term show that the entire embryonic myocardium differentiates uniformly for a period and, then, the differentiation diverges on two dissimilar lines : one resulting in the general myocardium and the other leading to the formation of the nodal and connecting systems.

The atrioventricular connecting system

The atrioventricular bundle is the first part of the specialized musculature to develop. It can be identified in the dorsal wall of the atrioventricular canal at the 7.5 mm. stage, before fibrous tissue invasion of the canal wall has commenced. As numerous mitotic figures are not present in the bundle anlage or in any adjacent tissues, there is no evidence to suggest that the bundle is formed by active proliferation.

The bundle develops too late to be held responsible for the conduction of the cardiac impulse in the initial contractions, which occur during the third week of gestation. It is perhaps more likely, as Waterston (1918) has suggested, that differentiation of the bundle is associated with the re-routing of the circulation, which occurs *pari passu* with ventricular septation. Initially, when the heart is a straight tube, the cardiac contractions pass from the sinus venosus to the atrium, then after a pause to the ventricle and, subsequently, to the bulbus cordis. However, as the interventricular septum develops, the bulbus (right-ventricle) comes to lie ' in parallel ' rather than ' in series ' with the ventricle (left ventricle). The formation of the atrioventricular bundle and its two branches enables the cardiac impulse to reach both ventricles almost simultaneously. However, even in postnatal life, the impulse reaches the left ventricle fractionally before the right ventricle. Thus in neonatal infants the left ventricle contracts before the right ventricle (Wood, 1956) ; it is only after the left ventricle undergoes physiological hypertrophy, presumably increasing the time taken for its excitation, that the two ventricles contract synchronously.

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[4] DeHaan (1961), noting that muscular contraction is not easily evoked in many parts of the myocardium, particularly in the postnatal heart, has suggested that the majority of myocardial cells are from the onset incapable of contraction, unless stimulated by another source ; he believed that the source is the specialized musculature. However, by DeHaan's own admission " . . . this conclusion may be premature when applied to the embryo, in view of the apparent lability of pacemaker function in immature myocardium ".

Sanabria (1936) considered that the common bundle, which differentiates in the dorsal wall of the atrioventricular canal, migrates through the dorsal endocardial cushion and fuses with the crest of the interventricular septum, which it induces to differentiate into bundle branches. However, it is clear that the dorsal canal wall is always in continuity with the muscular septum and that the process of differentiation spreads uninterruptedly from the canal wall to the septum, forming the common bundle, the bundle branches and the subendocardial networks. The burial of the bundle within the fibrous trigone, which Sanabria interpreted as migration by the bundle, is the result of passive displacement by subepicardial fibrous tissue.

The atrioventricular node

The atrioventricular node develops at the atrial end of the common atrioventricular bundle, after the latter has differentiated. In other words, the node is a further specialization of the bundle. Hence, it is unlikely that nodal differentiation is associated with the factors initially inducing the development of the bundle. Since the node forms only when nerve fibres reach the nodal site, it may well be that these nerves are responsible for its differentiation. Because the cardiac impulse must, under normal circumstances, always pass through the atrioventricular nodal region, the latter is an advantageous site for the establishment of nervous control over atrioventricular conduction.

Although the atrioventricular node initially lies in a symmetrical position between the right and left atria, its relations are altered by changes in the fibrous trigone. When that segment of the trigone, which lies between the attachments of the interatrial and interventricular septa, is moulded in line with both septa, the node is shifted towards the right atrium (see fig. 12) near the coronary sinus opening. Another result of this reorientation is that the node comes to lie on the right dorsal aspect of the aortic vestibule. Although the developmental changes in the atrioventricular region shift the node, the tendon of Todaro (1877) is always a reliable guide to the nodal position. This tendon is formed by condensation of connective tissue in the sinus septum. From the sinus septum, it arches over the node to be attached to the fibrous trigone.

The sinus node

The sinus node develops at about the 20 mm. stage by differentiation of the musculature of the right sinus horn near the mural attachments of the septum spurium and the right venous valve. Owing to the formation of the interatrial septum secundum, the cranial pole of the node is usually pulled into the superior interatrial sulcus. The resultant angulation can cause the node to be cut twice in the same section and serial sections are necessary if it is to be correctly interpreted as a single structure.

According to Mackenzie (1913), the consistent localization of the node to the sulcus terminalis is a result of the obliteration of the intersepto-valvular space ; this obliteration was held to disrupt the left arc of the sinu-atrial ring with the result that the specialized tissue is restricted to the base of the right venous valve. The ontogenetic findings reported here do not support this concept because from its earliest appearance, when the intersepto-valvular space is still present, the sinus node is restricted to the right horn of the sinus venosus and is unrelated to the left venous valve. The phylogenetic evidence also does not support Mackenzie's hypothesis because Davies (1931) and Walls (1943) have shown that in certain animals the limitation of the sinus node to the sulcus terminalis coexists with a wide intersepto-valvular space.

The more likely explanation for the consistent localization of the sinus node is that, within the embryonic sinus venosus, the right horn is the dominant region and is the source of the cardiace impulse (De Haan, 1959). When the sinus node differentiates, it does so at the site of maximum innervation of the right sinus horn, which is already the pacemaker for the heart.

SUMMARY

1. The development of the specialized cardiac musculature has been studied in serial sections through the heart in ninety-one human embryos and foetuses, ranging from 4 mm. to 310 mm. C. R. length, and in two neonatal infants.
2. The atrioventricular bundle commences to develop in the dorsal wall of the atrioventricular canal at about the 7. 5. mm. stage. By the time the interventricular septum is completed, both bundle branches have formed. Subsequently, moderately swollen muscle fibres differentiate in the subendocardial layers of each ventricle, in relation with the corresponding bundle branch.
3. The atrioventricular node, which is a further specialization of the atrial extremity of the bundle, develops when the nerve fibres reach the nodal site. Subsequently, the node which initially lies between the two atria, is shifted towards the right atrium, near the coronary sinus orifice, by moulding of the fibrous trigone.
4. At the 20 mm. stage, the sinus node arises precisely at the site of maximum innervation of the right sinus horn, near the mural attachments of the septum spurium and the right venous valve.

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EXPLANATION OF PLATES

Plate I

Fig. 1 7.5 mm. C. R. embryo (H & E). Section through the heart showing the compact fasciculus (b) of cells in the dorsal wall of the atrioventricular canal merging with the musculature at the crest of the interventricular septum (I.V.S.) ×51.

Fig. 2 Enlargement from fig. 1, showing a mitotic figure in a cell within the compact fasciculus. ×500.

Fig. 3 10 mm. C.R. embryo (H & E). Section through the heart showing that, at this stage, the junction of the right common cardinal vein (R.V.) and the the right sinus horn (R.S.) is quite distinct from the sinu-atrial junction which is demarcated by the attachments of the venous valves. ×36.

Fig. 4 10 mm. C.R. embryo (H & E). The compact atrioventricular bundle (b) passes between the dorsal atrioventricular endocardial cushion (e.c.) and the interventricular septum (I.V.S). Note the strand of fibrous tissue at the base of the left atrioventricular cushion (l) interrupting the continuity of the atrial and ventricular musculatures. ×36.

Plate II

Fig. 5 16 mm. C.R. embryo. Reconstruction showing the position of the atrioventricular bundle (b). At its atrial end, it is loosely arranged forming the nodal primordium (a) at the base of the conjoined interatrial septum primum and sinus septum. The bundle passes behind the right atrioventricular opening and extends along the crest of the interventricular septum ×45.

PLATE III

Fig. 6 13.5 mm. C.R. embryo (Bodian stain). Section through the heart showing the atrioventricular bundle (b). At its atrial end, the bundle merges with the primordium of the atrioventricular node (a) which is a loosely arranged mass of cells. ×33.

Fig. 7 16 mm. C.R. embryo (Bodian stain). The atrioventricular bundle (b) stands out from the adjacent interventricular septal myocardium because of its compact arrangement. ×30.

Fig. 8 20 mm. C.R. embryo (Bodian stain). A section through the heart showing the primordium of the sinus node (S) at the base of the right venous valve. ×100.

Fig. 9 Diagram of the fibrous skeleton of the heart depicting the positions of the atrioventricular node (a) and bundle (b) The tendon of Todaro arches over the node. x—the contribution to the fibrous trigone by the subepicardial tissue which thus pushes in and buries the bundle within the trigone.

Fig. 10 48 mm. C.R. foetus. (Bodian stain). Section through the heart showing the sinus node. The slender nodal cells are oriented round the nodal artery. A bundle of nerve fibres lies at the surface of the node (see arrow). ×100.

PLATE IV

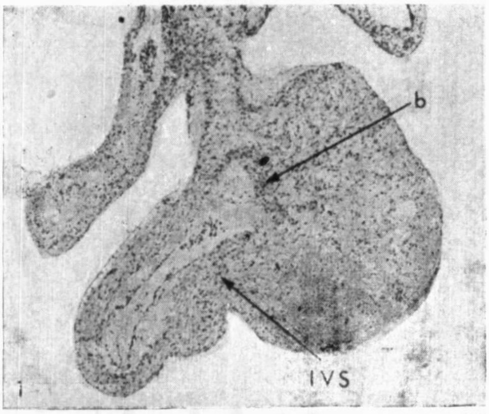
Fig. 11 48 mm. C.R. foetus. Reconstruction showing the sinus node lying on the ventral and right aspects of the superior caval inlet (S. V. C.). The nodal artery arises from the right coronary artery and traverses the axis of the node. The right pulmonary artery (r.p.a) is closely related to the dorsal aspect of the caval inlet. ×30.

PLATE V

Fig. 12 Diagram depicting the the developmental changes in the orientation of the atrioventricular node (a) and bundle (b). A-approximately the 20 mm. stage. The node lies at the bases of the interatrial (1 & 2) and sinus septa. Note that the interventricular septum is attached to the trigone well to the right of the attachment of the interatrial septa. B-100 mm. stage. Part of the fibrous trigone is moulded into line with the interatrial and interventricular septa thus forming the atrioventricular septum (A.V. septum). This process shifts the node towards the right atrium.

Fig. 13 76 mm. C.R. foetus (Margaret Long stain). Section through the heart showing the close relationship of the tendon of Todaro (T.T) to the atrioventricular node (a). ×36.

Fig. 14 93 mm. C.R. foetus (Cresyl violet). The left bundle branch (l.b.) merges with the general myocardium about halfway down the interventricular septum. b-common trunk of the atrioventricular bundle. ×36.



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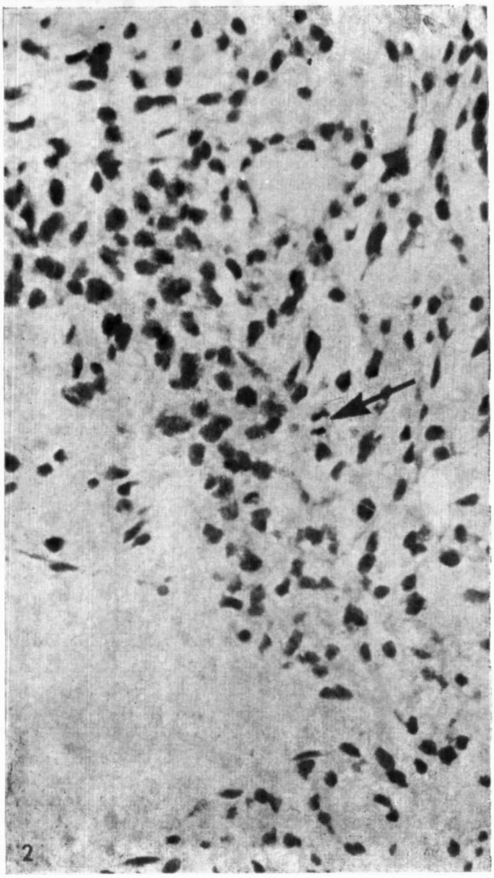

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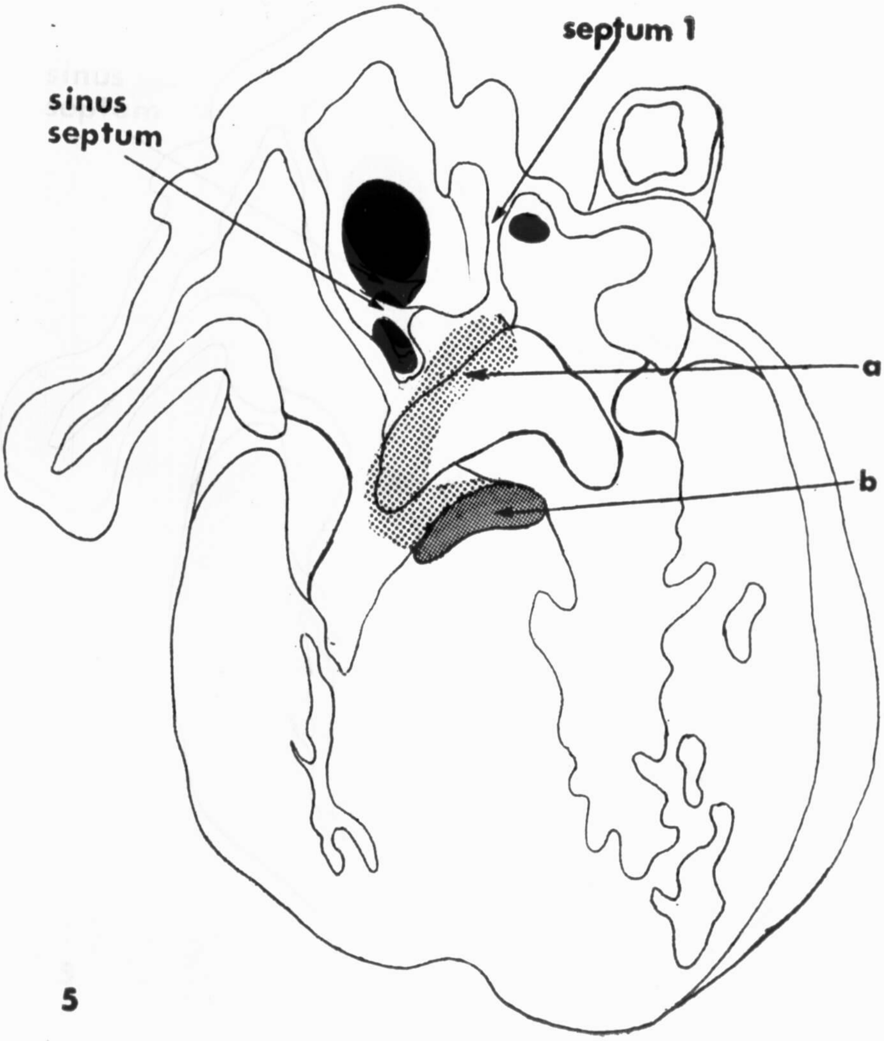

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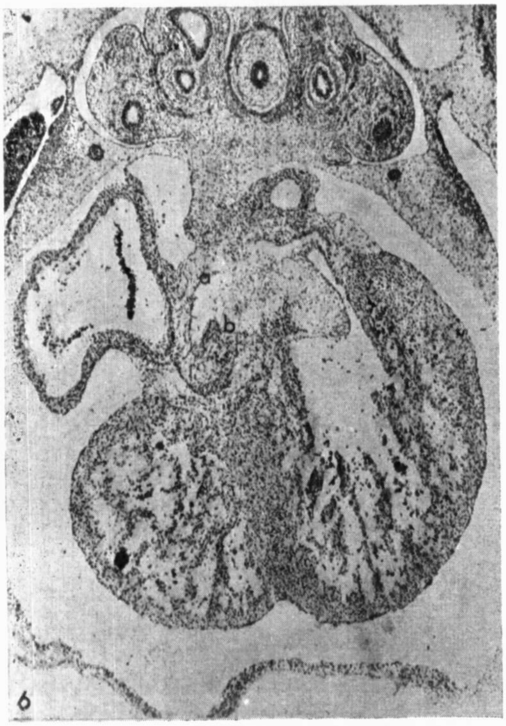
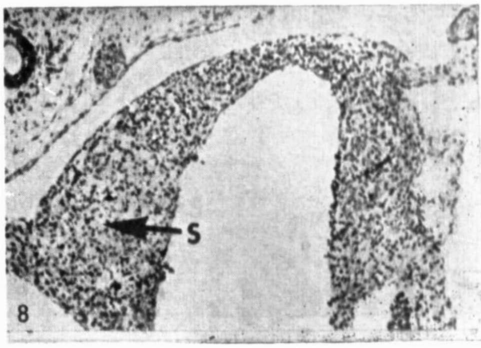
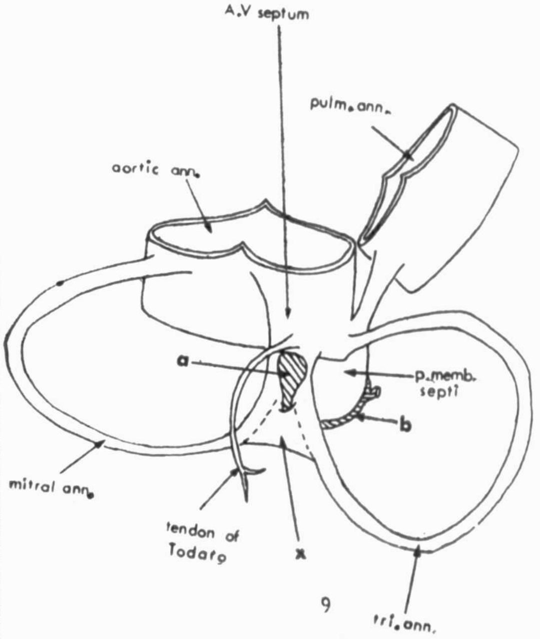
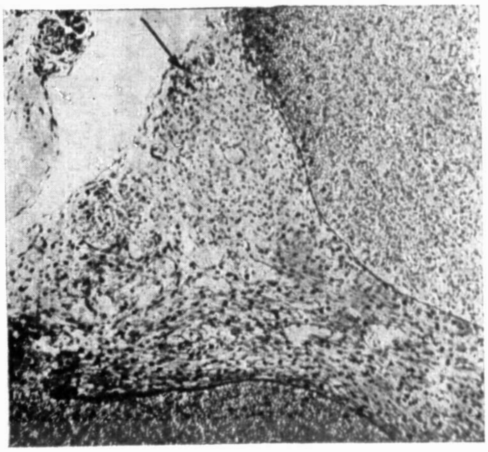

a
b
6


S
8


A.V septum
pulm. ann.
aortic ann.
a
p. memb. septi
a
b
mitral ann.
tendon of Todaro
x
tri. ann.

9


b
7



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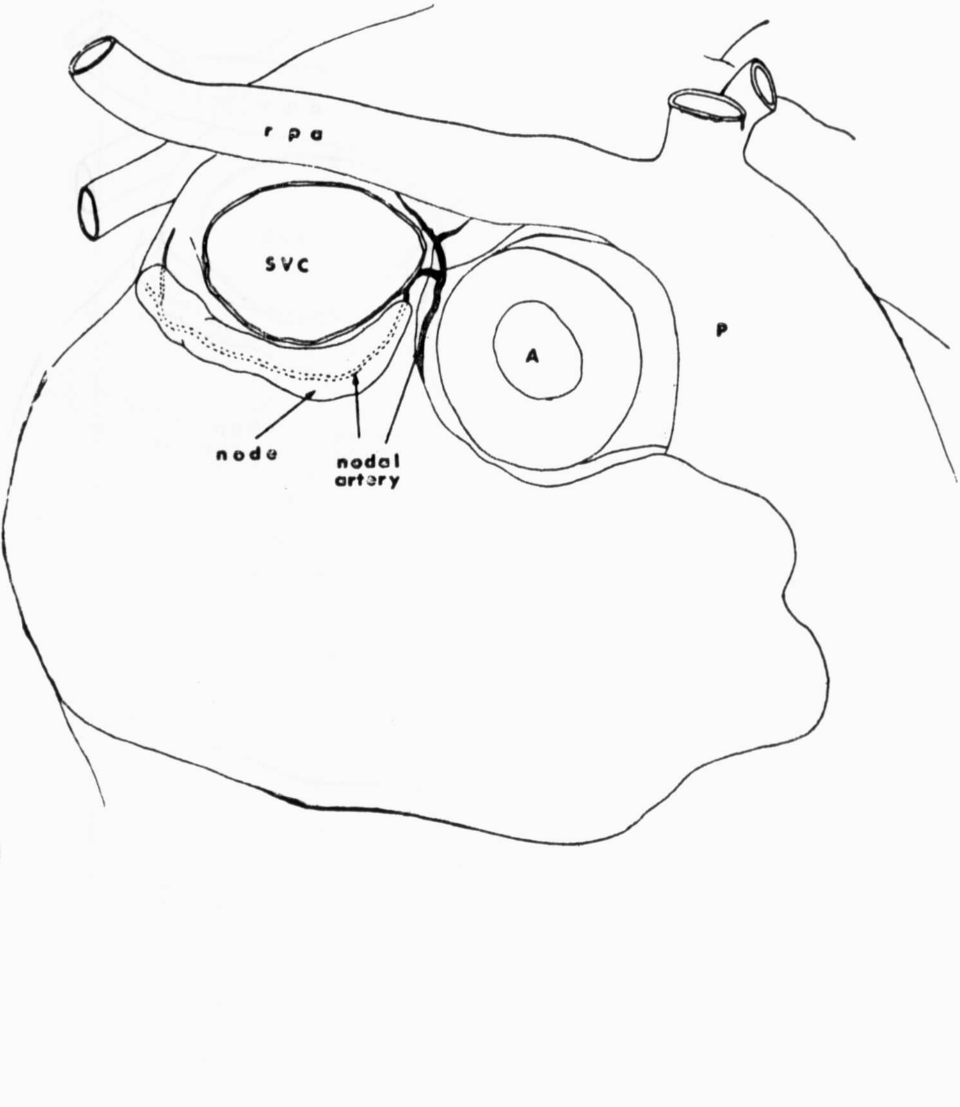

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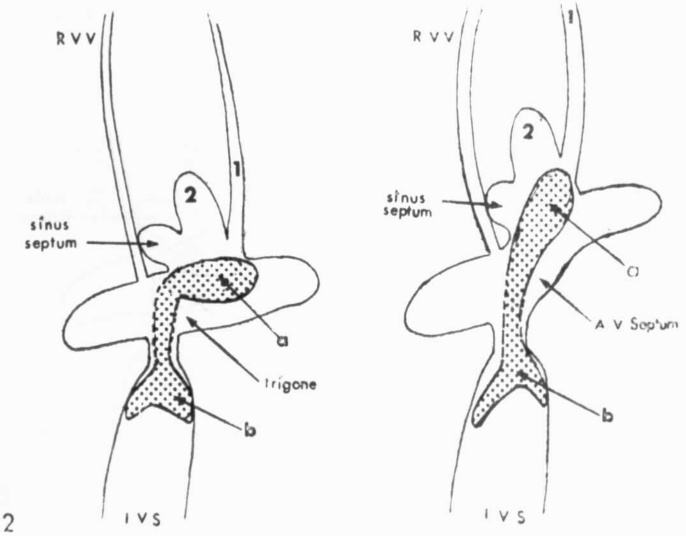
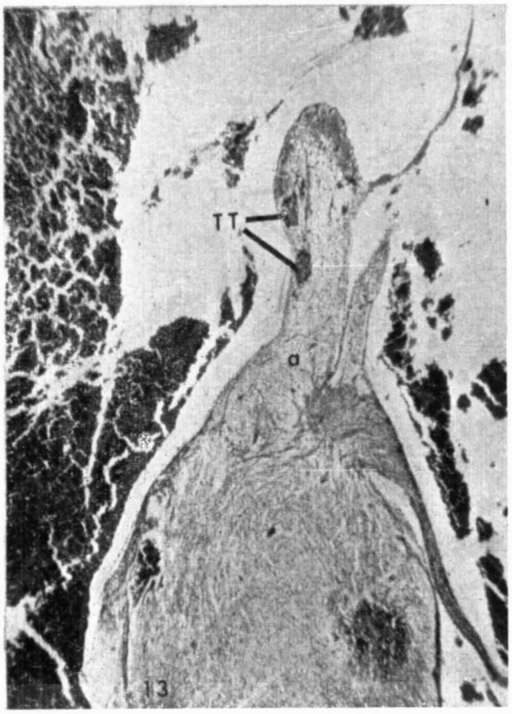

RVV
1
2
sinus septum
a
trigone
b
IVS
R V V
1
2
sinus septum
a
A V Septum
b
I V S

12


TT
a

13


b
I b

14