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OBSERVATIONS ON THE SINO-VENTRICULAR CONNECTING SYSTEM OF THE MAMMALIAN HEART.

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WITH THREE FIGURES.

The literature of the so-called atrio-ventricular bundle of His has been so recently and so exhaustively reviewed by Tawara, Mönckeberg and others that it seems unnecessary at this time to do more than give a very brief survey of the history of the so-called bundle, reviewing somewhat more in detail the work of a few writers who have investigated the aspects of the subject with which my own work has especially dealt.

In 1845, as is well known, Purkinje first called attention to the presence in the subendocardial layer of the sheep's heart of a network of gray, flat, mucoid fibers, probably muscular in nature, partly on the papillary muscle, partly on other fibrous bundles and partly bridging folds and clefts in the heart wall. These fibers, which have always been known as Purkinje's fibers, were described by numerous writers in the half century following Purkinje's observations and they were noted, not only in the sheep heart, but also in that of pig, calf, goat, horse, dog, cat, rat, mouse, goose, hen, dove, and even in the human heart in the newborn infant by Henle and as late as 15 years old by Gegenbaur. They were usually found subendocardial, but were described also in the myocardium and by Hoffman in the pericardium.

In 1893, His, Jr., in mouse, dog and man discovered a bundle of muscle fibers arising in the posterior wall of the right auricle near the auricular septum in the auriculo-ventricular furrow, running along the upper edge of the ventricular septum musculature forward and dividing into a right and left branch which extend down into the ventricular septum and soon end by fusing with the ventricular muscle, thus connecting the auricular and ventricular musculature. In 1904, this observation was confirmed by Retzer, who saw the bundle in cat, rabbit and rat, as well as in dog and man. He found the course varying slightly, but always connected with auricular muscle and merging into the ventricular at a short but variable distance from the point of division of the bundle. He estimates that in the human adult the bundle is about 18 mm. long, 2.5 mm. wide and 1.5 mm. thick. In 1906, Tawara made the most important contribution to our knowledge of this connecting muscular link between auricle and ventricle when he showed not only the presence of the bundle in every one of a large number of species of mammalia investigated, these including human embryo, child and adult, but also showed that the bundle ended, not as previously thought, by fusing immediately with the ventricular muscle, but by branching and spreading out into a complicated system of terminal fibers throughout the entire lower portion of the ventricles, these being the well known Purkinje fibers; that the bundle recognized by His and Retzer and the Purkinje fibers were but parts of a great complicated system of muscular fibers connecting auricle and ventricle. His results were confirmed in all important points by Keith and Flack in 1906, by Retzer, Fahr and Mönckeberg in 1908. Retzer showed that the system developed in the pig from the sinus which originates in the right and left venous valves and grows down in crescent-shaped lamellæ into the lumen of the right atrium. The left venous valve attaches itself to the atrial septum, the right divides into the Eustachian and Thebesian valves. The sinus fibers then grow down through the septum intermedium to the right and left sides of the interventricular septum where they become the highly differentiated structures—the Purkinje fibers. He suggests the term sino-ventricular conducting system, which is divided into the sino-ventricular bundle and the Purkinje fibers. In 1907, Fahr published a communication in which he confirmed Tawara's findings in the sheep heart but not in the human heart, in which he stated that the right and left limbs ended without branching, both in the embryo and in the adult, thus confirming the earlier findings of His and Retzer. However, in 1908, he modified his views, bringing them more in accord with the findings of Tawara. In this last work he reconstructed a portion of the interventricular septum with the bundle fibers of a three-year-old child. His model shows the left limb branching and sending twigs toward papillary muscles and growing down toward apex of heart and losing itself in the trabecular network. The right limb, however, he still represents as unbranched. In a twelve-year-old child however he finds slight but not extensive branching of the right limb also, but explains the difference between his findings and those of Tawara as due to a possible individual variation. Fahr was unable to recognize the bundle earlier than in a 16 cm. embryo and could see no branching of the bundle until later than this. Mönckeberg however (1908) traced the bundle and its two main limbs clearly in a 7.5 cm. human embryo and in a 16.5 cm. human embryo notes histologic differences between the bundle fibers and those of heart muscle and also notes the division of the left limb into several branches which he could trace through the trabeculæ to the papillary muscles. The right limb, however, showed no branching in this series. According to Mönckeberg's investigations, this conducting system is found constantly in the human embryo from 7.5 cm. on. It varies slightly in its course in the atrium and with respect to its relation to the left and right surfaces as it passes through the annulus fibrosus and later in its terminal branching. The development, therefore, proceeds from sinus region downward into ventricle and later into the complicated system of Purkinje fibers.

An especial interest has attached to the study of this sino-ventricular system (1) because of the importance assigned to it by physiological experimentation and (2) because of its relation to certain well known but little understood pathologic and clinical conditions. The heart physiologists were divided into two classes, the neurogenists and the myogenists, the former believing that the contraction and rhythm of the heart were due to nerve influence, while the latter ascribed them entirely to muscular action. The neurogenists based their theory (1) on the well known and generally accepted fact that nerve cells are the natural originators of all impulses and nerve fibers the natural conductors of such impulses; (2) on the generally accepted absence of all muscular connection between the auricles and ventricles, at least in the higher mammalia, by means of which impulses could be conducted. The myogenists, on the other hand, rested their case on the early contractility of the heart, before the development of nerve elements and on the contractility of the heart in certain invertebrate forms in which a nerve mechanism in the heart seemed to be entirely lacking. The absence of a muscular connection between auricles and ventricles was an important missing link, however, in their chain of reasoning, by which they attempted to show that the impulses began in the sinus region and from there were carried to all parts of the heart in regular sequence and rhythm, the entire mechanism being muscular. This missing link was supplied by the discovery of this small connecting bundle of muscle fibers and it was at once seized upon by the myogenists to complete the chain of evidence in support of their theory. Humblet and Hering, by cutting the bundle, showed a dissociation of the auricular and ventricular rhythms, while Erlanger, by clamping the bundle, was able to cause either a partial or complete heart block, gradual or sudden, and also to bring the heart back to normal by loosening the clamp. His brilliant results seemed to establish beyond cavil the function of the bundle as conductive and as co-ordinating the auricular and ventricular rhythm and the muscular nature of its action seemed proved by Retzer's statement that no nerve fibers were included in the clamp and also by the declaration of His that no nerves run in the bundle. However, the presence of nerves in the bundle has been demonstrated conclusively by Tawara and others and later admitted by Retzer.

Clinicians and pathologists had long been interested in a disease described by Stokes and Adams and known as Stokes-Adams disease, in which the cardiac manifestations were similar or identical to those caused by experimental cutting or clamping of the bundle. It was therefore assumed that a pathologic affection of the bundle was responsible for this clinical affection and numerous pathologic hearts have been subjected to investigation with reference to the condition of this connecting bundle. Among the most noteworthy contributions to the literature along this line are those of Tawara, Aschoff, Fahr and Mönckeberg.

Soon after the publication of Tawara's monograph, at the suggestion of Dr. Huber, I undertook an investigation of the sino-ventricular connecting system, especially with reference to verifying by reconstructions Tawara's findings regarding the extent and complexity of the system and its connection with the Purkinje system of fibers. Later publications have perhaps diminished the necessity for such verification, but the growing importance of the subject and the growing interest in its embryology, morphology, physiology and pathology will justify the presentation of my results. My investigations have been carried on by careful gross dissections of the system in sheep, calf and man, by wax reconstructions in man, calf and lamb and by histologic study in man, dog, sheep, calf and cat after different methods of fixation anl staining, including the structure of the fibers themselves and of the connective and elastic tissue surrounding them, and the nerve distribution and supply.

My first model, shown in Fig. 1, represents the upper portion of the bundle in the adult human heart reconstructed by the Born plate method as modified by Mrs. Gage, paraffined absorbent paper of the required thickness being used instead of wax plates. The model is 25 times the size of the bundle and is reduced in the figure to about one-tenth the size of the model. The posterior extremity of the main trunk of the model represents the anterior portion of the Knoten, which will be described later, the remainder of the Knoten and its posterior extensions, where the outlines were less clear because of fusions with the auricular muscle, not being represented in the model. The actual length of the undivided trunk of the bundle, so far as shown in the model was 11 mm., the diameter varying considerably, being 1.6 mm., 2.8 mm. and 4.4 mm. in different parts. The division into two limbs taken place, as is usual, near the point of union of the posterior and median aortic valve flaps and at the upper extremity of the ventricular muscular septum, so that the right and left limbs begin as subendocardial strands, separated by the narrow cone of ventricular muscle which is usually found at this place in the human heart. The left limb is broad and thin, broadening more and more as it passes downward following the curve of the septal wall and always subendocardial. It divides at a distance of 21.2 mm. below the point of bifurcation of the main bundle into

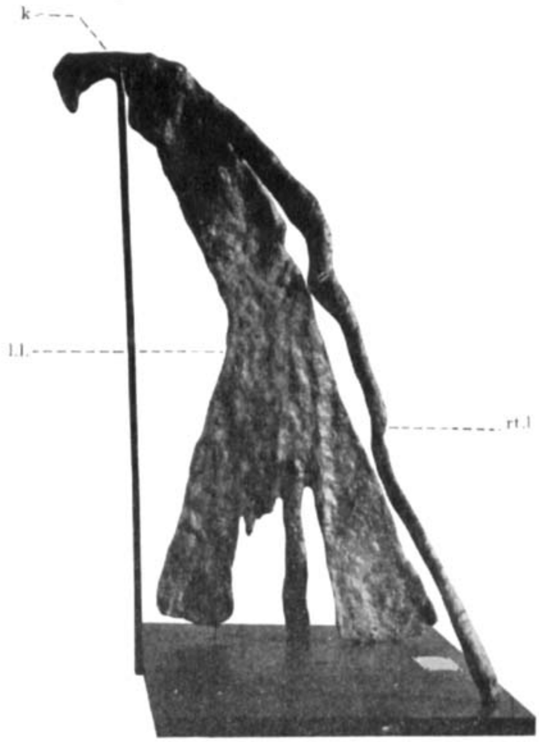

FIG. 1. Wax plate model of human sino-ventricular bundle 25 times magnified, reduced in figure to one-tenth size of model. k is Knoten; rt.l., the slender right limb; l.l., the broad left limb with first branching, into ant., post., and median branches.

three branches, the anterior and posterior branches being broad, while the mesial branch is much slenderer. These all continue subendocardial to the end of my series of sections and hence to the end of the model. The right limb is much smaller than the left and almost cylindrical, varying in diameter from .8 mm. to 1.6 mm. It is at first subendocardial, but, as the septum thickens, this limb becomes surrounded by septum musculature and passes at first downward and forward and but little outward deep in the septum musculature for a distance of about 25 mm. It then turns sharply outward and its course is then downward and outward and but little forward for a distance of about 10 mm., when it reaches the endocardium. Here my series ends, near the point where the moderator band, or as Retzer more appropriately terms it, the trabecula supraventricularis, leaves the septum and carries the right limb of the bundle with a large mass of septum musculature to the anterior right papilla. The model represented in Fig. 2 represents the upper portion of the bundle in the lamb's heart 50 times magnified, but it is reduced in the figure to about one-twelfth the size of the model. It was made by the Born wax plate method and begins in the Knoten. Posterior to this point, the connection with the auricular muscle was so close and the outlines of the bundle so poorly marked on the auricular side that it was difficult to outline it with sufficient accuracy for reconstruction. The Knoten was from 1 to 1.5 mm. in diameter and 4 mm. long. At the neck where it passed through the annulus fibro-cartilagineus, it changed rather abruptly to a diameter of from .3 to .4 mm., enlarging again somewhat in the ventricular portion of the bundle. The narrowed neck portion was about 1 mm. in length and the bundle then extended downward and forward in the muscular interventricular septum about 4.6 mm., before it divided into the right and left limbs. The left limb then extended directly downward and outward to the endocardium on the left side of the septum, a distance of 3.4 mm., where it divided into two branches, an anterior and a posterior, the latter showing a small median branch near its beginning. These remain subendocardial to the end of the model. The unbranched subendocardial portion of the left limb was from 1.4 to 1.8 mm. in length and from .1 to .2 mm. in thickness. The right limb passes downward and forward and outward, a distance of 5 mm., until it reaches the endocardium where the series of sections ended. The right limb measures from .8 to 1.2 mm. in width and from .4 to .6 mm. in thickness, so that it approaches more nearly to the cylindrical form. The further course of the right and left limbs and their branches will be discussed further a little later in this paper. These two models show the course of the main trunk of the bundle, the Knoten and the upper portion of the right and left limbs to be very much as had been represented by His, Retzer and Tawara. The block of human heart tissue serially sectioned for the model was something over 35 mm. in length and I realized at this time that a reconstruction of the sino-ventricular bundle with its terminal expansions would require serial sections of the entire ventricle with a portion of the auricle; that these sections would need

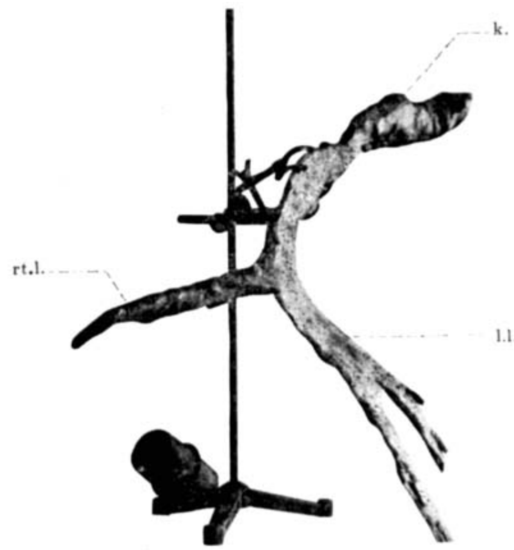

FIG. 2. Wax plate model of lamb's sino-ventricular bundle. k is the Knoten with main bundle. rt.l. is the upper portion of right limb, and l.l. the left limb with upper portion of branches.

to be relatively thin and to be magnified from 100 to 400 times in order to bring out the fine terminal ramifications of the bundle with any accuracy. Unwillingly recognizing the practical and economic difficulty and even impossibility of such a task in the larger hearts, I attempted to dissect out the bundle with its terminal ramifications and found that by the constant aid of a hand lens and the frequent aid of the microscope, the sino-ventricular system could be followed, not only in its subendocardial course, but also for some distance into the muscle, while it was comparatively easy to dissect out the main limbs and to trace them back to the trunk and Knoten and to the beginning in the sinus region. Still desiring to make graphic as accurate a representation as possible of this entire connecting system, I conceived the idea of making a reconstruction from such a dissection. With the patient and skillful aid of Miss Gertrude Welton, one of my students, the model represented in Fig. 3 was constructed in the following manner. Choosing a young beef heart in which the differentiation between heart muscle and that of the sino-ventricular system was well marked, the entire heart was fixed in Kaiserling's solution, the ventricles being first filled with the solution and the heart then suspended in the Kaiserling's solution, in order to prevent the distortion which frequently follows fixation in the ordinary way. The apex and outer wall of the left ventricle were then removed, leaving the anterior and posterior left papillæ in situ. The right ventricle was then opened carefully from above down posteriorly, without cutting the trabecula supraventricularis or destroying any of the apical connections between septum and outer wall. Starting with the easily seen left limb, removing the superficial layer of the endocardium, the dissection of the main bundle, Knoten and upper portion of the main limbs was relatively easy. The dissection of the terminal ramifications was then carried on with needles, constantly using the hand lens and, when in doubt, the microscope, until the entire system was exposed, so far as it was possible to differentiate it from the cardiac muscle. Then lengths, diameters and angles were carefully measured at every point, the measurements multiplied by ten, a wire skeleton was constructed and covered with wax, all angles and measurements being retained, as nearly as possible in the same proportion. Hence the model represents a ten-fold magnified sino-ventricular system of the beef heart, as accurately as a hand lens and gross dissection can show it. The connective tissue sheath was not always entirely removed, since that would often mean the complete disintegration of the bundle; hence the threads and especially the nodes represent these portions of the system with the most closely adherent connective tissue. As seen in this model represented in Fig. 3, which should be viewed through a stereoscope, the main bundle begins in the region of the coronary sinus by the union

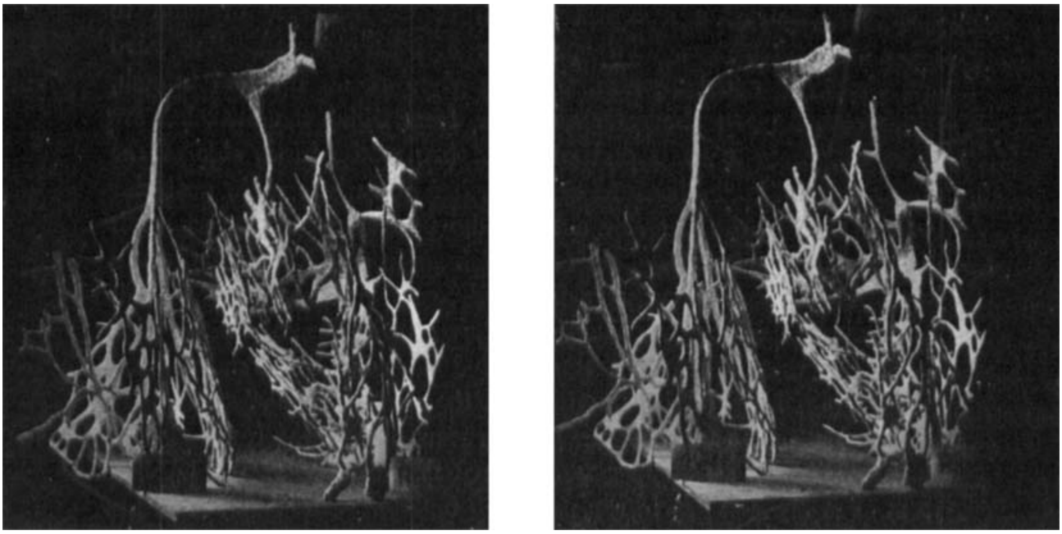

FIG. 3. Stereoscope photograph of model of sino-ventricular system in calf's heart. To be viewed through stereoscope.

of two portions, the origin of one of which seems to be lost in the mass of fat, connective tissue, nerve fibers and ganglion cells, which are found in the region of the sinus, while the other can be traced upward for a short distance and is then lost or merged in the auricular muscle. Some connections with the auricular muscle at the sides and upper part of the Knoten are not represented. The actual length of the bundle to the point of division was 33 mm. The point of division lay at the upper margin of the interventricular septum as in the human and not deep in the septum musculature as in the sheep heart. The left limb was therefore subendocardial from the beginning, while the right limb lay buried under about 1 mm. of muscle. After passing about 38 mm. almost vertically downward from the point of division, the left limb divides into two main branches, an anterior and a posterior. The anterior and posterior branches pass each into a fibro-muscular strand or false tendon, these crossing the ventricular cavity to the anterior and posterior papillæ. About 2 mm. beyond the point of division, the posterior branch gives off two long slender branches to the septal wall, which anastomose with branches from a septal branch of the anterior division to form a septal plexus. The posterior division proceeds downward and backward about 20 mm. when it gives off an internal branch, which soon forms a characteristic node, from which five branches are given off, three to the septal wall and two to the inner side of the posterior papilla. About 12 mm. further down, the main posterior branch reaches the anterior side of the posterior papilla, where it divides into two branches, each of which again subdivides, the resulting branchings frequently fusing with each other or with strands from other divisions into characteristic node-like forms, which again break up, thus forming a complicated network, surrounding and penetrating the papilla, sometimes on the surface and often deep in the muscle. One long slender branch runs around the inner side of the papilla and could be traced nearly to the apex of the papilla, most of it buried deep in the papillary muscle. Occasional branches are given off from the papillary network to join the septal network, which will be more fully described later. The papillary branches could be traced as independent strands nearly to the apex of the papilla, where they were lost or became continuous with the papillary muscle. The anterior papillary division, about 3 mm. below the point of its formation, gives off a large septal branch, while the remainder passes downward and forward without further branching to the anterior papilla, where it divides into three main branches, one of which is slender and passes around the septal side of the papilla near its apex; the other two are of nearly equal size, the one external and the other internal. Both subdivide a number of times, the resulting twigs anastomosing with each other at intervals to form the characteristic node-like forms which were before described, in which the component fibers lose their identity in a mass of connective tissue, containing large numbers of the so-called Purkinje fibers. This then breaks up again into separate independent fibers, some of which again enter into a node and again divide, the whole forming a plexus-like arrangement over the entire posterior surface of the anterior papilla. In the heart from which this model was constructed, the outer wall of the left ventricle was removed for convenience of dissection, so that the network which we know to have been present on this wall and to have been derived from branches of the papillary divisions, is not shown in the model. The septal wall of the left ventricle both between the papillæ and where it curves around behind the papillæ is covered by a network of Purkinje fibers, similar to the network described on the papillæ and formed of the anastomosing subdivisions of septal branches of the anterior and posterior divisions of the main limb, which have already been described. These form the node-like forms described, which, with their connecting strands make up the network. Occasional small branches pass back from the anterior and posterior papillary plexuses to the septum and join with the septal branches to form the septal plexus. The plexus described covers well the septal surface to the level of the branching of the main left limb and even sends some fine filaments higher on the septal surface. The right limb is narrower and more nearly cylindrical than the left and approaches the endocardium slowly. It runs at first downward and outward and a little forward and then downward and forward and a little outward. After an unbranched course of about 42 mm. in the septal wall, it enters the moderator band or trabecula supraventricularis, which in this heart was about 23 mm. long, making the total length of the unbranched right limb 65 mm. I was unable to find any branches given off from this limb before it reached the anterior papilla, which it entered on its anterior surface about 28 mm. below its apex. Here it bifurcated, one branch passing forward to the outer wall of the right ventricle, while the other passed backward on the papilla. Both of these branches break up into a large number of smaller branches, which form nodes and redivide and form a plexus similar in all respects to that described on the left side. Some of these branches could be traced upward on the exterior wall nearly to the base of the ventricle, some running quite deeply in the ventricular muscle, but most of them in the endocardium just under its superficial layer. One branch passed around the papilla on its septal side nearly to its apex, while another passed on its peripheral side, the two nearly encircling the papilla near its apex. From the plexus described in the outer wall of the right ventricle and the anterior papilla on that wall, three main branches pass back to the right surface of the septum and the broad flat posterior papilla which is closely attached to the septum and presents only a short blunt head projecting forward and upward from its septal attachment. These branches reach the posterior part of the septal wall, redivide, form nodes and again break up, so that the entire right surface of the septum to about 20 mm. from the base is covered with an intricate network of these terminal branches of the sino-ventricular system. While this model represents the ramifications and distribution of the system in only one heart, careful gross dissections of other calf hearts and also of human and sheep hearts have shown beyond question that the distribution shown in the model may be regarded as typical. The main bundle may be longer or shorter, may be a little more to the left or right of the position shown in model and in the sheep, as before stated, passes down some distance into the interventricular septum before dividing. In all cases investigated, however, the bundle divided into two limbs, the right passing unbranched to the anterior papilla, where it divided into either two or three branches, from which a network similar to that shown in the model spread out over the papilla, the outer wall and the septum, while the left limb divided into either two or three branches, the anterior and posterior passing to the anterior and posterior papillæ and forming networks, while the median, if it exists, or if not, septal branches of the anterior and posterior divisions form a septal network. The general course was the same, but slight modifications were found, not only in the hearts of different species, but also in those of different individuals of the same species.

In the complicated course described and modeled, branches of the system often cross, not only narrow clefts between columnæ carneæ, but also the entire ventricular cavity by means of longer or shorter trabeculæ, which resemble connective tissue and are known as pseudotendinous threads. Tawara and Mönckeberg have made these threads the subject of exhaustive research, especially with reference to their abnormal course in the left ventricle of the human heart in various pathologic conditions. Tawara defines these abnormal tendon threads as "bundles of the atrio-ventricular system which have become loosened from the walls and pass freely through the ventricular cavity." Mönckeberg, however, after study of numerous pathologic conditions, concludes that not all trabeculæ crossing the ventricular cavity between the septum and the papillæ carry branches of the atrio-ventricular bundle. He divides them into three main classes: A. Threads having no muscle at all, but consisting of connective tissue—true tendon threads. B. Threads carrying both myocardial fibers and fibers of the atrio-ventricular system. C. Threads carrying only fibers of the atrio-ventricular system with their connective tissue sheaths. In order to determine whether this classification in abnormal human hearts might apply also to normal animal hearts, I examined microscopically all threads, long and short, crossing the ventricular cavity in two beef hearts. Since the results seemed uniform, with very slight variations in the number and course of such threads, I will describe in detail the threads found in only one of these hearts.

A. From the upper portion of the septal wall in the neighborhood of the valve insertion, three or four fine threads passed to the papillæ, being inserted in or near the apices of the papillæ. These threads consisted of connective tissue only and contained no muscle fibers, so that they may be regarded as belonging to Mönckeberg's Class A.

B. In the left ventricle, the following threads were found:

1. Between middle or lower part of posterior left papilla and septum below valve level.

a. Large strand from about 24 mm. below septum membranaceum to about 8 mm. below apex of papilla, with two fine subbranches back to septum.

b. 5 mm. lower, a smaller strand with two subbranches, one to septum and one to lower trabecula.

c. Short slender thread 7 mm. lower, with one subbranch to septum and one connecting with thread No. 2.

2. Between middle and lower part of anterior left papilla and septum below valve level.

a. Large strand from 30 mm. below septum membranaceum to 15 mm. below apex of papilla. No subbranches.

b. 4 mm. lower, smaller thread with two subbranches to septum.

c. Small thread 4 mm. lower with one subbranch.

All of these threads were examined microscopically and all were found to contain connective tissue, blood vessels and nerves and larger or smaller fibers belonging to the sino-ventricular system. All except two very fine ones contained also some myocardial fibers.

3. On the right side, the main moderator band or trabecula supraventricularis was the only connection between the anterior papilla and the middle part of the septal wall and this had no branches. The posterior right papilla is a broad flat papilla closely attached to the septum and between it and the outer wall of the ventricle two main strands could be seen, each of which had several subbranches. All of these showed both myocardial fibers and fibers of the sino-ventricular system, as well as numerous nerves and blood vessels and connective tissue.

C. The two threads found on the left side, which contained no myocardial fibers, but only sino-ventricular fibers, connective tissue and nerves and blood vessels.

From the limited number of investigations I have thus far been able to make on these threads, therefore, I would conclude that in the heart of the calf at least, as Mönckeberg has shown in the human heart, true tendon threads are found connecting the upper part of the septum with the apices of the papillæ; that below the branching of the main limbs of the bundle, all the pseudo-tendinous threads crossing the ventricular cavity carry branches of the sino-ventricular system.

I find also that the great majority of them may be regarded as belonging to his Class B, carrying both myocardial and sino-ventricular fibers, while only one or two very fine, short ones belong to Class C, carrying no myocardial fibers. I also find that all the threads of Classes B and C carry, in addition to the muscle fibers, small blood vessels and bundles of nerve fibers, the latter running in the connective tissue around the sino-ventricular branch and often sending finer nerve bundles between its individual fibers. Retzer regards the so-called false tendons in the pig as always bridges for the conductive system, this including both Purkinje fibers and nerve fibers.

Histology of Sino-ventricular System.

The earlier writers on the histology of the Purkinje fibers were divided into two great classes, (a) those who, with Purkinje, described two kinds of elements in the fibers, a network of cross-striped fibers resembling heart muscle, in the meshes of which were imbedded peculiar, clear mucoid cells, containing nuclei; b, those who believed that the Purkinje fibers consisted of short broad cells, whose center was clear and mucoid in character and contained from one to several nucleoid bodies, while the periphery showed cross-striped fibrils similar to those in heart muscle, thus having only one kind of element. Tawara, however, in his monograph, has described in detail the histology of the entire sino-ventricular system in sheep, dog, and man and his description with few modifications has been followed by all later writers. In all forms described, he divides the atrioventricular system structurally into two main portions, the auricular and the ventricular, each of which is subdivided into two parts: the auricular into the trunk and the Knoten, the ventricular into the upper undivided part and the terminal expansions or Purkinje fibers, the differences in structure being most marked in the sheep and least marked in the human heart, the dog being intermediate in the differentiation of this system. The Knoten in the sheep is described as a complicated network of small irregular fibers, which change as the bundle passes through the annulus fibro-cartilagineus, into large clear fibers, with peripheral fibrillation and central nuclei. This type becomes more pronounced when the limbs reach the endocardium and spread out in the terminal ramifications, which are known as Purkinje fibers and which later fuse with the myocardial fibers. Tawara describes the fibers of the main limbs and terminal expansions in the sheep heart as consisting of broad, short, irregular, polymorphous cells, two or three or more of which side by side are united to form cell strands, which at intervals anastomose with other cell strands forming often node-like structures, the whole appearing as a complicated network in the meshes of which are found connective tissue, fat, blood vessels and nerves. The fibril bundles are mostly at periphery of the cells and run uninterruptedly from one cell to another in the cell strand. In the terminal expansions, the clear centers are more pronounced and the meshes of the network longer and narrower. In spite of the continuity of the fibril bundles, Tawara regards the strands as consisting of separate and independent cells connected by intercellular fibrils comparable to those in the epithelial cells of the epidermis. In dog and man, he finds the auricular portion of the system similar to that in the sheep, while the ventricular portion is less sharply differentiated by reason of the more extensive development of the fibrillar structures. In the new-born dog, the fibers of the bundle consist of short broad cells with clear nucleated centers and fibrillated borders, very similar to those in the sheep, while in the adult dog he finds "sarcoplasmic territories" with distinct limiting zones, so that in the dog also he regards the Purkinje fibers as consisting of cells with connecting fibrils, the fibrillar structures being more developed and more uniformly scattered throughout the cells than in the sheep. In the human heart, the Purkinje fibers are even less clearly differentiated from the myocardium than in the dog's heart, but he regards them as cellular rather than syncytial because of the presence of cross lines which are arched or wave-like, rather than step-like as in the myocardium and completely divide the fiber, between two nucleated areas; he also finds some of the fibril bundles stopping at the cross lines while others pass through. The careful and detailed description given by Tawara has been accepted by other authors with very little modification. Retzer denies the existence of a Knoten in the pig's heart, stating that he finds the network-like structure ascribed to it by Tawara throughout both the auricular and ventricular portions of the system. Mönckeberg, in his excellent monograph on the atrio-ventricular system in the human heart, questions Tawara's view that the cross lines seen in the Purkinje fibers of the human heart represent cell outlines, although he admits the presence of separate independent short polymorphous cells with clear nucleated centers and narrow peripheral fibrillar zone in the sino-ventricular system of a 16.5 cm. human embryo. He states that the development of fibrils results in the formation of solid star-like or fusiform structures with anastomosing processes forming a network, with vesicular cells forming the meshes. Later the solid portions unite into tube-like fibers with occasional connecting branches, this process being carried further in the limbs than in the Knoten, where the network structure is preserved. An interesting communication by Aschoff reporting the work of his student Nagayo, calls attention to the glycogen content of the sino-ventricular system. In the beef, calf and sheep heart, he finds glycogen constantly present and characteristically distributed, either diffusely scattered in the interfibrillar portion or as numerous large granules in the perinuclear sarcoplasmic area, except in the Knoten, where there is but little. In the goat also it is constantly present, but mostly diffuse. In the pig, corresponding with Retzer's finding of the extension of the Knoten structure into the ventricle, he finds very little glycogen and almost limited to the terminal expansions. In the human bundle, the results were variable; thirty hearts were investigated, of which three showed distinct glycogen content, nine very small amount of glycogen, and eighteen almost none. The dog's heart with reference to the glycogen content of the sino-ventricular system, resembles the human heart, if we regard the large amount of glycogen as the normal condition. Mönckeberg also investigated the glycogen content of the sino-ventricular system in the human heart at different ages and under different pathologic conditions and, like Aschoff, finds it variable, a fact which he ascribes to pathologic conditions or to poor condition of tissues. He concludes that myocardial fibers are always glycogen-free in post-uterine life, while in the Purkinje fibers it is constantly and characteristically present, though diminished in atrophic and cachectic conditions and that glycogen stains may be used in properly fixed hearts as a means of differentiation between Purkinje fibers and myocardial fibers. The main points of variance then are (1) as to the presence and histologic differentiation of such an auricular structure as is designated by Tawara as the Knoten; (2) as to whether the ventricular portion of the system and especially the Purkinje fibers are syncytial or cellular in structure.

In my investigation of the histology of the sino-ventricular system I have studied the hearts of sheep, both young and adult, of calf, of dog, including a 6 cm. embryo, a 3-day old puppy and an old dog, of cat and of man. I have used the ordinary hematoxylin and eosin and hematoxylin and Van Gieson stains, also the Schultze chrom-hematoxylin, the Heidenhain iron hematoxylin, the silver, the Mallory connective tissue stain, the Weigert elastic tissue stain, and also the methods recommended by Heidenhain for the study of heart muscle. In all these types the most constant and typical structure found was the network in the auricular portion of the system designated by Tawara as the Knoten. This in all cases consisted of an intricate network of fibers, which varied greatly in size, but the average size of which was much less than that of the auricular muscle or of the rest of the sino-ventricular system; the nuclei are smaller and more numerous than in the auricular muscle. The anastomosis of the fibers takes place, not by simple fusion of two uniting branches, as is usual in heart muscle, but by the formation of nodes or star-like forms, into which two or three or more fibers become merged and from which a variable number of fibers emerge. In the node, the fibers completely lose their identity, fibrils from the different fibers commingling confusedly. Surrounding the Knoten and in the meshes of its network are found connective tissue, blood vessels and many nerve fiber bundles, especially in the lamb and calf heart, with numerous ganglion cells in the calf's heart and a few were seen in the sheep's heart. In the sino-ventricular system of the sheep and calf, this small-fibered network changes rather abruptly, shortly before the bundle passes through the annulus fibro-cartilagineus into a large-fibred network, the change beginning in the central portion of the bundle. The ventricular portion of the sino-ventricular system is markedly different in the different species examined. In the sheep and calf, where the fibers are most typical and most clearly differentiated from the myocardial fibers, the fibers are much larger than the myocardial fibers, with fewer fibrils and much more sarcoplasm. The fibrils are grouped into larger and smaller bundles, which run partly in the direction of the fiber and partly cross it in devious directions, forming a network which encloses certain clearer areas in which are found one or several nuclei. Tawara regards these as independent cells joined together to form cell strands, but even in the sheep, in which the apparent cell outlines are most distinct, the fiber appears to me as a syncytium, a continuous mass of sarcoplasm, through which run the bundles of cross-striped fibrils in different directions, dividing up the sarcoplasmic mass into clearer non-fibrillar areas, containing one or several nuclei and three to six of which make up the transverse diameter of most of the fibers. The fiber bundles themselves anastomose at intervals, forming a network in the meshes of which are found connective tissue having many more elastic fibers than are found between the myocardial fibers, blood vessels and nerves. These rarely penetrate the fiber strand and then only a short distance. In the calf, ganglion cells were found in these meshes throughout the entire distribution of the system, but I have been unable to duplicate this finding in the hearts of other species examined. My reasons for believing that the fibers of the sino-ventricular system are syncytial in character are (1) the fibrils and fibril bundles pass uninterruptedly through the fiber in different directions, forming a more complicated fibrillar network throughout the fiber than could be accounted for by any other hypothesis than that the fiber is the unit of the system; (2) I have been unable to find white or elastic connective tissue fibers penetrating the fiber, or dividing it, except a few peripheral strands which are easily explained as following the irregular contour of the fiber strand. Also no blood vessels or nerves seem to penetrate the fiber bundle; (3) I have occasionally seen clefts such as were mentioned by Tawara, but believe them to be due to shrinkage of the sarcoplasm during fixation. The cell-like forms or sarcoplasmic territories are very variable in form and size and separated simply by strands of cross-striped fibrils. In the terminal expansions of the system, the fibers, if cut longitudinally, appear oblong and occasional cross bands are seen, not unlike those in the myocardium, but either straight or slightly curved or arched, rarely step-like as in the myocardium. In dog, cat and man, the fibers of the ventricular portion of the sino-ventricular system more nearly resemble the myocardial fibers, being differentiated from them by being broader and paler and less fibrillar and more vacuolated, large, clear nucleus-containing areas resembling those in the sheep being not infrequent. The nuclei are smaller and less frequent than in the myocardium, although occasionally two or more are seen in a single sarcoplasmic territory. The cross lines are distinct and often cross the entire fiber, but may occur at frequent intervals, the short space between them being non-nucleated, or they may be widely separated, several nucleated spaces occurring between two such bands; this finding was noted also by Mönckeberg. The fibers are very variable in size and nodal points showing a commingling of fibrils from different fibers are frequent. The appearance varies somewhat with the direction of the section, a section tangential to the endocardial surface showing much broader fibers with larger perinuclear areas than one vertical to the surface, showing that the fibers are broader than they are deep, the broader dimension lying parallel to the endocardial surface. Connective tissue and especially elastic fibers are much more abundant than in the myocardium. In the 3 cm. dog embryo and also in the 3-day old puppy the fibers appeared as independent cells, sharply outlined by blue lines in the Mallory stain, an outlining which was never brought out in the adult condition. Hence my findings in the embryo and newborn agree with those of Tawara and Mönckeberg as to the fact that Purkinje fibers are composed of single short clear cells, but in later life, at least in man, dog, and cat, and probably also in sheep and calf, the fiber bundle seems to me syncytial.

Transitions from the fibers of the sino-ventricular system to the myocardial fibers are rarely seen in my sections; this is explained by the fact that the transition is very gradual, so that only rarely would a section follow a fiber through the entire transition from a typical Purkinje fiber to a typical myocardial fiber. Beginnings and endings of the transition are frequently seen, and in one or two instances I have been able to trace the entire process. It is impossible to say from my sections, however, whether all the fibers of the sino-ventricular system end by fusion with the myocardial fibers or not.

Nerves. Tawara states that he finds the sino-ventricular system of the calf accompanied throughout by numerous large nerve bundles, which are intimately associated with the muscle bundles and even in the ventricular portion of the system contain ganglion cells. He also finds small nerve bundles in the sheep heart, but no noteworthy nerve bundles in man, dog, or cat, though he admits that quite fine nerve bundles may accompany the system in all species of animals. Mönckeberg states that in the human sino-ventricular system he finds no nerve elements or forms resembling such, though he used many special methods for their demonstration. Wilson, after examining the atrio-ventricular bundle in calf, sheep and pig, states that he finds in it, in addition to the special form of muscle fiber, an important and intricate nerve pathway, consisting of:—

(1) Numerous ganglion cells, mono-polar, bi-polar and multi-polar, whose processes pass either to other ganglion cells in the bundle, to the muscle fibers of the bundle, or through the bundle so far as examined.

(2) Abundant nerve fibers running through the bundle in strands and either ending in ganglion cells in the bundle, or in the muscle plexus, or passing through the bundle, so far as examined.

(3) An intricate plexus of varicose fibrils around and in close relation to muscle fibers of the bundle.

(4) An abundant vascular supply with well-marked vaso-motor nerves and sensory endings.

Retzer, on account of the presence and close relation of nerve fibers to bundle fibers in pig's heart, regards the system as a neuromuscular end-organ, a conclusion with which Wilson does not agree, since he finds the essential anatomical structure of a neuro-muscular spindle,—shape, lymph spaces, lamellar capsule, as well as nerve endings,—lacking in the sino-ventricular system, while ganglion cells are present in the system and absent in the neuromuscuar spindles.

In the calf's heart, the nerve bundles are so large and prominent, not only in the Knoten, but also throughout the distribution of the sino-ventricular system, that they are readily seen in preparations stained by ordinary methods, and it would be impossible in this heart to question the prominent part which nerves and ganglion cells play in the structure and probably in the function of the sino-ventricular system. They are not only in the connective tissue sheath, but smaller bundles run between the fibers and appear to stand in more or less intimate relation to the fibers of the system. In the hearts of young lambs, and to a less marked extent also in those of older sheep, the nerve fiber bundles also follow the entire distribution of the system, although few ganglion cells could be seen in it, after the bundle passed through the annulus fibro-cartilagineus. In the hearts of dogs, cats and men, larger nerve bundles were more rarely seen, and then only in the connective tissue sheaths of the system, and very small fiber bundles or single fibers only are seen between the single fibers and it is usually difficult to distinguish any nerve fibers between the muscle fibers of the terminal expansions. I have studied the nerve distribution in lambs' hearts with the intravitam methylene-blue method and found larger nerve bundles in the sheath, breaking up into smaller bundles and finally into a network of single fibers, which appeared to end on the muscle fibers of the bundle, although nerve terminations were not satisfactorily demonstrated. It would appear that the nerve supply is independent of that in the immediately surrounding myocardium, since in some of my preparations very few of the nerve fibers surrounding the myocardial fibers were stained, while the nerve fibers of the sino-ventricular system were well stained throughout its entire distribution in the ventricular as well as in the auricular portion. Ganglion cells also were found so that my findings corroborate those of Wilson in every particular. The question of the nerve and blood vessel distribution, however, I desire to leave for further investigation, the results of which will be published with those of investigations on other phases of the subject in a later communication.

Regarding the function of the sino-ventricular system, my investigations have had little to do. That it has a function independent of that of the myocardium seems assured from the constancy of its presence in all species studied, the relative constancy of its structure and distribution, the probable independence of its blood and nerve supply, the relatively constant and typical glycogen content, as shown by Aschoff and Mönckeberg, and its independent pathology, as shown by Tawara, Mönckeberg, Fahr and others. That its function is conductive, or at least coordinative, seems probable, both from physiologic experimentation and from pathologic study. Whether it may also originate impulses and thus account for the independent ventricular rhythm established after severance of the connection between auricle and ventricle, and whether its function is muscular nervous or neuro-muscular, must be left for further study and experimentation. Because of the large number of nerves and their intimate relation to the muscles, at least in some of the species studied, the neuro-muscular hypothesis seems to me the most probable and it may be possible that it is called into action by the distension of the ventricles and the stretching of the endocardium.

In conclusion I desire to thank Dr. Huber for suggesting the subject of this investigation and for the kindly interest he has shown in its progress; also I wish to express my appreciation of the skill and patience with which Miss Gertrude Welton aided me in the construction of the model; I am grateful also to Drs. Novy and Streeter for their aid in photographing the models.

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