Differentiation of the Atrioventricular Conducting System of the Heart

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The structure and function of the atrioventricular conducting system of the heart, and its relationship to the myocardium, are examined from a developmental point of view. On the basis of information derived from electron micrographic, electrophysiologic, and developmental studies of heart tissue, it is concluded that: (1) The idea of the syncytial nature of the heart lacks a sound anatomic basis. (2) Cytdifferentiation during embryonic cardiogenesis results in the development of at least 2 distinct populations of cells: those comprising the bulk of the myocardium and a second type, the specialized cells of the conductive tissue, which differs in histology, biochemistry, and physiology. (3) The common view of the myocardium as a spontaneously active tissue may require revision, since several lines of evidence appear to indicate that myocardial cells are quiescent until stimulated by an extrinsic source. Under normal circumstances, this stimulus source is the conductive tissue.

The developmental physiologist is interested, not only in the changing functions and interrelationships of organs and tissues in the embryo, he is also concerned with the application of information and concepts obtained from the fields of developmental biology to problems of adult physiology. The problem of the structure and function of the atrioventricular conducting system of the heart is particularly interesting when examined from a developmental point of view.

In the early embryonic heart, the endocardium and epicardium are separated by a thick gelatinous layer, the "cardiac jelly." Distributed through this matrix are mesenchymal cardiac myoblasts, from which the bulk of the myocardium and, presumably, the conductive tissue will form. As the myoblasts begin to differentiate, taking on the characteristics typical of heart muscle, the conducting tissue becomes progressively more easily distinguishable. This divergence may be interpreted in two ways. One is that it results from the simultaneous development of the conductive system and myocardium along dissimilar paths of differentiation. It is often stated, however, that conductive tissue is only "specialized" myocardium in which certain properties, for example conductivity and spontaneity, are exaggerated. Authors taking this position usually note that these properties are "embryonic" in character. Thus, the second possibility is implied: that the two tissues are basically similar during embryogenesis, differentiating along the same route, but at different rates. At any given stage of development, the conductive system should then be less highly differentiated than the surrounding myocardium, but should not exhibit any qualitatively different characteristics.

We find ourselves concerned, then, with the degree of difference between myocardium and conductive tissue. Are fibers of these two types characterized by distinct histologic, cytologic, and biochemical properties? Do such differences underlie clear-cut physiologic differences of more than a quantitative nature? Do myocardial and conductive fibers, in fact, constitute two different tissues?

I shall examine these questions by drawing upon the literature concerning the physiology and development of the heart of various mammals, and of the chick embryo. Numerous investigators have noted the basic similarities in cardiac development of these forms.

Histodifferentiation

During the early period of cardiogenesis, curvature and differential growth change the heart from a primitive straight tube to a complex S-shaped organ in which the four adult chambers are clearly represented (fig.
1). The beat is initiated at the posterior end of the heart. As the primordial atrioventricular (A-V), atrial, and sinoatrial (S-A) regions progressively form, each of them, in turn, takes over the pacemaker function, initiating the beat for the entire heart. At these early stages the primordial atrial and ventricular muscle are in direct continuity around the entire circumference of the A-V canal. A stimulus arising in the sinoatrial region should be able to spread throughout the heart, freely to all areas. That this is true has been demonstrated by Patten who cut away all of the tissue around the A-V canal of a 4-day chick heart except for a narrow connecting strand (fig. 2).* This strand then served as an "artificial bundle" to conduct the sinoatrial rhythm to the ventricles. He found that it made no difference whether the connecting strand was left at the site where the normal bundle would later develop (marked with an asterisk in fig. 2), or whether the strand was left on the opposite wall of the heart.

During the fifth and sixth weeks of human development, endocardial and epicardial connective tissue gradually encroaches on the myocardium at the A-V sulcus and invades this connecting zone. The separation of the atria and ventricles is ultimately completed all the way around the sulcus, as the primordial fibrous skeleton of the heart is formed. However, early in the sixth week of development (9 to 10 mm. human embryo), a compact cluster of cells makes its appearance in the posterior wall of the A-V canal, toward its right side.† This is the A-V node, in cellular continuity with the atrial muscle above and narrowing into the A-V bundle below. The bundle runs across the top of the thick interventricular septum, behind and under the dorsal endocardial cushion (fig. 3). At this stage relatively little cytologic differentiation has yet occurred in either the node or

*Figure 2 reproduced from Patten: Univ. Michigan M. Bull. 22: 1, 1956. By permission of the Michigan University Medical Bulletin.
†Figure 3 reproduced from Walls: J. Anat. 81: 93, 1947. By permission of the Journal of Anatomy.

bundle. The bundle, of course, is not invaded by the encroaching connective tissue and remains as the single fascicle of conducting fibers connecting the atria and ventricles. Within a week or 2, the bundle branches arise, and the node and bundle become clearly distinguishable from the surrounding myocardium as pale-staining meshworks of cells with rounded nuclei, containing scattered and poorly striated myofibrillae (fig. 4). As they approach the apex of the heart, both the left and right bundle branches ramify into progressively smaller groups of fibers with much interlacing and "anastomosis."§, 6

The cells of the branches, proximally, are similar histologically to those of the bundle itself, which in turn resemble nodal cells. As
the branches ramify distally, they become swollen and "watery," exhibiting a central juxtanuclear hyaline space, peripheral poorly formed myofibrils, and scattered mitochondria; that is, they become typical Purkinje fibers (fig. 5). In the human embryo, such fibers do not appear until rather late, probably between the tenth and fifteenth week of development (60 to 100 mm.)

However, by the end of the fetal period, a complex, interlacing basketwork of specialized fibers invades all parts of the ventricular musculature. A reconstruction of the entire ventricular conducting system is shown in figure 6, which is a retouched photograph of a model made by Lydia DeWitt. It shows the A-V node, bundle, branches, and the major ramifications. The fine "terminal" Purkinje fibers are not shown. (Throughout this paper, the tissue comprising the S-A and A-V nodes, the bundle, branches, and Purkinje fibers, will be referred to as "conductive tissue.")

The consequence of all this embryonic histodifferentiation is the presence of two readily distinguishable types of fibers in the adult heart of most mammals and birds. Some of their respective properties are summarized in table 1, which compares certain histochemical and cytologic properties of typical myocardial, conductive, and embryonic heart cells.

In spite of their manifest differences, we should remember that many similarities also exist between myocardium and conductive tissue. Both types of fibers exhibit intercalated discs, striated myofibrils, sarcosomes, and other cytoplasmic inclusions characteristic of muscle. Both contain antigenic combining groups of cardiac myosin. Moreover, it is now generally accepted that they are also physiologically similar, in that all heart tissue is characterized by the 3 functional properties: contractility, conductivity, and spontaneity. Let me quote from 2 representative sources on this matter. In a recent paper on the "Microanatomy of Muscle," Walls states:

"Cardiac muscle tissue is found only in the heart and surrounding the mouths of the great veins which enter it. In some ways it resembles both voluntary and smooth muscle, yet in its rhythmic, unceasing activity from early embryonic life until death, it stands alone." (p. 52).

And, in his chapter in Fulton's Physiology, Nahum calls our attention to the fact:

"that all parts of the musculature of the heart are inherently capable of autogenic rhythmic discharge, and that the normal sequence of excitation is made possible only because the sinoatrial node possesses this capacity in a higher degree than any other region." (p. 672).

Thus we are told that the properties of cardiac muscle distinguish it clearly from other types of muscle, and also that heart muscle consists of a basically homogeneous population of fibers, all having essentially the same properties, showing only certain minor differences in degree in different regions.

The idea of the heart as a syncytium of fibers in cytoplasmic continuity tends to foster this concept of homogeneity.

Cellular versus Syncytial Structure

Early histologists considered heart muscle as cellular in structure and interpreted the intercalated discs as junctional zones of opposed cell membranes, staining heavily as a result of intercellular cement substance. For example, Eberth, to whom the first detailed description of the intercalated disc is usually attributed in 1866, regarded the discs as intercellular structures, not only on the basis
of their histologic appearance and their strong reaction with silver nitrate (known to stain cell membranes), but also because of the tendency of macerated heart muscle to fragment along the intercalated discs. Later, Ranvier24 also described mammalian myocardium as being composed of individual rhomboidal branching cells with centrally placed nuclei.

It was not until after the turn of the century that Heidenhain25 and Godlewski26 independently enunciated clearly the hypothesis that the heart was syncytial in nature. These workers felt that the discs represented either contraction artifacts or the sites of sarcomere differentiation. Perhaps the strongest proponent of the syncytial nature of adult myocardium was H. E. Jordan, who, over a period of a decade or more, published observations and strenuous arguments in support of this idea.27, 28 (It is interesting to note, however, that even Jordan was compelled to admit to the cellular structure of Purkinje tissue and of embryonic heart.)

The controversy over syncytium versus cells recurred periodically in the literature of the first half of this century, as some microscopists continued to make observations corroborating the earlier cell view.29 However, most investigators during this period gradually tended to accept the syncytial hypothesis and even extended it to the conductive tissue.29

Especially important in this trend toward the idea of a cardiac syncytium were the early demonstrations of the "all-or-none" response of heart tissue by Bowditch,31 Woodworth,32 and others. It was felt that this finding could best be explained on the basis of protoplasmic continuity between all cardiac fibers. During the last decade, also, confirmatory electrophysiologic evidence has been obtained. In 1951, Curtis and Travis33 reported that bundles of Purkinje fibers in the false tendon of the ox heart responded to electric stimulation in an all-or-none manner, that is, the demarcation potential, measured between the cut end and the surface, remained at con-
constant amplitude with varying strengths of suprathreshold stimuli. Thus the fibers appeared to behave syncytially. This was further supported by measurements of specific core resistance of Purkinje fibers by Weidmann. He showed that, although the resistance of the cylindrical membrane surrounding a fiber was of the same order as that of muscle or nerve, the core resistance (i.e., the longitudinal internal resistance) was not appreciably higher than that of the sarcoplasm. He concluded that the intercalated discs do not form a significant barrier to ionic movement along the length of the fiber.

In spite of the evidence of homogeneity (and even identity) of all fibers, Thomas Lewis (1925), after some 20 years of pioneering work in cardiac electrophysiology, proposed his "law of cardiac muscle." In this statement, he noted that there are different kinds of heart cells: those characteristic of myocardium, and typical Purkinje fibers. Because of the prevailing opinions, this idea was not strongly favored, and few references to it appear in recent decades.

In the last few years, however, since electron microscopy has been applied to this problem, it has been shown repeatedly and without exception that the idea of a cardiac syncytium lacks a sound anatomic basis. Perhaps a dozen electron microscopists, using ever more sophisticated technics, have found that the intercalated disc does consist of a pair of apposed cell membranes, covered with densely staining granules. The myofibrils do not cross the intercalated discs, nor is there any other evidence for any kind of protoplasmic continuity across the membranes. Each elongate cell of a myocardial fiber is consistently observed to be surrounded by an intact plasma membrane (for recent review of evidence see 34). This is true in both myocardium and conductive tissue. Moreover, the pattern of development of the intercalated discs in cardiac myoblasts, at the sites where the myofibrils are interrupted by cell membranes, also supports the idea of a cellular structure. Thus, neither in the embryo nor in the adult heart; neither in myocardium of cold-blooded or warm-blooded vertebrates; nor in nodal or conductive tissue is there a satisfactory anatomic basis for the notion of syncytial structure.

A Functional Syncytium?

The studies of Curtis and Travis and of Weidmann noted above, led to the use of the concept of heart tissue as a "functional syncytium." By this it is implied that even though cardiac fibers do not, in fact, exhibit protoplasmic continuity, under certain conditions they behave as if they did. For example, in small cultured fragments (50 to 100 microns in diameter) of embryonic heart tissue, the membrane effects of a polarizing

Figure 3

Section through the heart of a 10-mm. human embryo. Left. The bundle (A.V.B.) may be seen arising from the A-V node and passing into the base of the dorsal endocardial cushion. Right. Continuation of the bundle down the left side of the interventricular septum. K=right sinus valve; L=left sinus valve; C. S.=coronary sinus; S. Pr.=septum primum; D=dorsal endocardial cushion. (Hematoxylin-eosin stain. ×100.) (From Walls.)

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current applied through one of a pair of intracellular microelectrodes can be recorded in any cell of the fragment, even when the recording electrode is as much as 100 microns from that used for stimulation, and visible cell boundaries separate the two. Moreover, synchronous and identical diastolic depolarization and action potentials can be recorded from all cells of such a spontaneously beating clump.

However, other physiologic evidence is accumulating, which suggests that individual cells, or at least small regions of cardiac tissue, are capable of separate activity, independent of neighboring cells or regions. Embryonic heart, for example, can be disaggregated with trypsin into small cell clusters, from which transmembrane resting and action potentials can be recorded. Such recordings are similar in all respects to those obtainable from cells in the intact heart. Thus the electrical activity of these cells is clearly unaffected by cellular dissociation. Moreover, in the cooled adult mammalian heart or frog heart perfused with hypertonic Ringer-sucrose solution, it is possible to record spontaneous action potentials from one fiber, while a neighboring fiber is completely quiescent, or fires at a different rate. Similarly, Cervoni, West, and Falk, recording intracellularly from rabbit atrial preparations, found that, when such a preparation was stimulated at 7 to 8 beats/sec., atrial cells responded to every stimulus, while nearby cells from the S-A node responded only to every other stimulus. At a time when a nodal cell was still in its refractory period, a neighboring atrial cell was fully repolarized and capable of firing.

Thus the weight of anatomic evidence appears to support the concept of the heart as a population of discrete cells, separated transversely by intercalated discs. Whatever the normal mechanism of transmission of the impulse across the discs, physiologic studies show that such transmission can readily be disturbed, with the result that the individual cells or contractile units can exhibit their independent nature. The histologic differentiation described above would further suggest that there are at least two distinct cell types: that making up the bulk of the myocardium, and a clearly different, perhaps more embryonic type, which constitutes the conductive system. (Space does not permit mention here of the evidence for intermediate types.) It is evident that processes of cell differentiation leading to such histologic differences must be based upon changes at the biochemical level. Is there, then, any evidence of biochemical or physiologic differentiation between myocardial and conductive cells?

Biochemical Differentiation

Quantitative biochemical differences between myocardial and conductive cells are many (see Schiebler, for review). For example, conductive tissue contains more choline acetylase than does myocardium. Healthy adult myocardium is quite low in glycogen, whereas the rich concentration of glycogen in conductive tissue has been noted repeatedly and can even be seen with in-

Figure 4

Cross section of the A-V bundle (B) and root of the right bundle branch (RB) in the crest of the interventricular septum (IVS) of a 7-day chick embryo heart. (Phosphotungstic acid hematoxylin. X 300.)
travital staining in the living heart. Its abundant supply of glycogen would suggest that conductive tissue might be highly dependent on glycolytic metabolism, perhaps in lieu of a strong oxidative cycle. This idea is supported by the finding that conductive tissue has a much lower succinic dehydrogenase activity than does myocardium, and has a total oxygen consumption rate only one-fifth as great. It is also resistant to cyanide and to anoxia.

There are 2 enzymes or enzyme systems in conductive tissue that appear to be qualitatively absent from myocardium in most species. (It is recognized that such a claim, based upon negative evidence, is valid only within the limits of presently available techniques.) Although nonspecific cholinesterases are abundant in all heart cells, Mommaerts et al., were able to characterize an enzyme from the A-V bundle and bundle branches of beef heart as a specific cholinesterase, similar to that characteristic of nervous tissue. More recently, Carbonell confirmed this and localized the enzyme histochemically to cells of the conduction system in hearts of the human, dog, cat, guinea pig, rabbit, rat, sheep, and cow. Only in the rabbit were equivocal results obtained, in which scattered cells in the myocardium exhibited esterase activity that was nonspecific in its substrate specificity, but was inhibited by eserine (1 of the criteria for specific cholinesterases). In the other species mentioned, specific cholinesterase was limited to cells of the conduction system (fig. 7*).

The second enzymatic activity seen exclusively in conductive tissue is that responsible for a phenomenon termed "aberrant lipogenesis," and suggests a distinctive fat metabolism in this tissue. Recently Kuwabara and Cogan have shown that Purkinje tissue can synthesize sudanophilic fat when incubated in serum supplemented by oleic acid, a capacity not shared by ordinary cardiac muscle. This property depends upon the presence of (1) an intracellular sulfhydryl-requiring enzyme system, (2) serum, and (3) oleic acid or sodium oleate as a substrate. It is clear from their work that cells of the conductive system exhibit this enzyme, whereas those of the myocardium apparently do not.

It is interesting to note that many of the biochemical and metabolic characteristics distinguishing conductive tissue from myocardium are the same as those differentiating embryonic from adult heart. Heart muscle of the early embryo is rich in glycogen, and highly resistant to anoxia. It is also low in succinoxidase and cytochrome oxidase activity, and is relatively insensitive to cyanide poisoning. Conductive tissue is thus distinctly "embryonic," in sharing some of the cytologic, histochemical and biochemical characteristics of primitive heart. At the

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*Figure 7 reproduced from Carbonell: J. Histochem. 4, 87, 1956. By permission of the author and The Williams & Wilkins Co.
same time, however, it shows definite signs of having differentiated along an independent path, developing a distinctive morphology and biochemistry, with at least two enzymes not shared with myocardium.

**Physiologic Differentiation**

Does the physiology of myocardium and conductive tissue show a similar pattern; that is, do these 2 tissues exhibit some functions that differ only in degree, and others that are totally restricted to 1 or the other?

One well-known quantitative physiologic difference between myocardium and the conductive system is in conduction velocity. Since the observations of Erlanger, it has been accepted that the conduction tissue is capable of transmitting an impulse more rapidly than myocardial muscle (with the exception of certain specific areas, as at the atrionodal junction). In 1959, Draper and Mya-tu measured the rate of conduction through specialized fibers in false tendons, and in the bundle branches, at a velocity of 2 to 3 meters/second. In contrast, strips of parallel myocardial fibers not containing Purkinje tissue were able to conduct the stimulus at a rate of only 0.5 to 0.6 meter/second. Clearly this represents a differentiation of new membrane characteristics by the specialized fibers to permit such rapid conduction, since embryonic myocardium starts out with a low conduction rate comparable to that which is apparently retained by adult myocardial muscle.

A second difference between myocardial and conductive cells, at a physiologic level, lies in the configuration of their action potentials. Intracellular recording from cells in various parts of the conductive system reveals action potentials that, when compared with those from myocardial fibers, have a
Specific cholinesterase activity in conduction tissue of the adult human heart. A. Subendocardial Purkinje fibers. B. A-V bundle and left branch. (From Carbonell.)

low amplitude with little or no overshoot, a low rising velocity of the upstroke, and long duration with a rounded plateau. In contrast to the steady resting potential common to myocardial fibers, recordings from pacemaker regions also show a characteristic slow diastolic depolarization of 10 to 20 mv, termed the "prepotential" by Bozler. The prepotential, in association with pacemaker activity, differentiates extremely early in cardiac development, long before specialized nodal or conduction tissue is histologically distinguishable. Recently Meda and Ferroni have been able to insert intracellular electrodes into hearts of chick embryos only a few hours after initiation of the beat. Even at these early stages (see fig. 1 A and B), cells showing a slow diastolic depolarization were found in the S-A region, while cells in the ventricle showed steady resting potentials similar to those from adult myocardium (fig. 8*). Thus, embryonic ventricular cells even in the 13-somite chick embryo, do not originate their own beat but are stimulated by cells in more posterior regions, which are acting as pacemakers.

This leads us to the final physiologic property that I should like to compare between myocardium and conductive tissue: the property of spontaneity, or pacemaker function. We have seen that in the embryonic heart, ventricular cells do not initiate their own beat but are driven by other cells. It is commonly accepted, also, that in the adult heart the contraction stimulus arises in the definitive pacemaker, the S-A node, and is transmitted to all parts of the heart via the fibers of the conduction system. Yet, as noted earlier, the idea that all heart muscle is characterized by the property of spontaneity seems to pervade the thinking of most cardiac physiologists, and it is stated explicitly in textbooks and other reference sources. Evidence appears to be accumulating, however, which suggests that the ability to generate bioelectric potentials, i.e., the pacemaker function, may not be a property common in varying degrees to all heart cells, but may be limited exclusively to cells that differentiate into some component of the conduction system. Myocardium, in contrast, appears to be completely quiescent until stimulated by an extrinsic source, in a manner analogous with skeletal muscle.

It should be emphasized that a systematic analysis of this problem has not been carried out, and decisive experiments are few. However, I should like to consider some of the
relevant data. In 1910 Erlanger showed that equal-sized strips of cat atrium, isolated in vitro, may be spontaneous or not, depending on what region of the atrial tissue is included. Strips of the left atrium frequently remained quiescent, while similar areas of right atrium, or of left atrium connected to the interatrial septum, usually showed spontaneous activity. We now know that those areas which Erlanger found it necessary to include in a strip if it was to beat spontaneously are the regions from which pacemaker prepotentials have been recorded; namely, the interatrial septum, the crista terminalis, the entrance of the superior vena cava, and the S-A ring bundle.

Evidence that spontaneity is limited to a portion of the cells of the heart arises also from observations made on such cells in tissue culture. Cavanaugh disaggregated 4- to 6-day embryonic chick hearts. She found that immediately after the cells attached to the glass substratum only 9 per cent showed spontaneous activity. Within the first day or two after the cells had spread and established extensive filopodial interconnections, the proportion pulsating rose to about 50 per cent. Moreover, as interconnections were established in the culture, cells that had been quiescent, or beating independently, could be influenced by a dominant neighbor to contract in synchrony with it. Other examples of such pacemaker activity by embryonic cells or heart fragments exist in the literature, and Harary and Farley have recently shown similar behavior on the part of dissociated cells of young (nonembryonic) rat hearts. Thus it seems reasonable to conclude that in neither embryonic nor adult heart is the majority of cells capable of spontaneous contraction. It is recognized, however, that this conclusion may be premature when applied to the embryo, in view of the apparent lability of pacemaker function in immature myocardium. Cells in the embryonic ventricle in situ do not show pacemaker prepotentials. However, cell clusters from this tissue, in culture, beat spontaneously and do exhibit slow diastolic depolarization. Thus, pacemaker activity in ventricular cells may be lost or suppressed during development of the intact heart but may be regained by at least some cells when isolated and subjected to culture conditions.

In adult heart, however, spontaneity does appear to reside exclusively in those cells that have differentiated into components of the conduction system. This argument has gained substantial strength from the recent observations of Draper and Mya-tu. These investigators confirmed the findings of many others by showing that muscle slips or papillary muscles from various mammalian hearts, maintained in vitro, are frequently not spontaneously active. However, they also noted that when such spontaneity is displayed, it "can always be traced to the presence of Purkinje tissue in the sample" (p. 107). For example, in one group of 18 ventricular muscle slips, 9 did not beat spontaneously,
yet all responded vigorously to external stimulation for many hours and showed normal resting and action potentials. These muscle slips were serially sectioned for histologic examination. Those that had not beat spontaneously showed no evidence of Purkinje tissue, while specialized fibers were found in all those that were active. Thus, we may conclude that in adult heart, if conductive cells are present to initiate an impulse (and possibly a critical number is required), we see "spontaneous" activity. Without these cells the heart muscle, though healthy and completely responsive, remains quiescent.

Conclusions

When information obtained from studies of the structural, chemical, and functional properties of the A-V conducting system of the adult and embryonic heart is considered, different conclusions may be drawn than those arrived at by a purely physiologic approach. Though not yet firmly established by decisive experiments, these conclusions appear to be reasonable in view of the evidence presented. They may be stated as follows: (1) Cellular differentiation during embryonic development of the heart leads to the presence of 2 distinct populations of cells: typical myocardial cells, comprising the bulk of the musculature of the heart, and the specialized cells of the conductive tissue. (2) Although cells of the conductive system do exhibit certain of the properties of embryonic myocardium, the two tissues in the adult may be distinguished by characteristic and unique properties, at the histologic, biochemical, and physiologic levels of investigation. (3) The differentiation of pacemaker function occurs very early in cardiac development. Within hours after initiation of the beat, and perhaps earlier, cells of the ventricle do not originate their own beat but are stimulated by other cells functioning as pacemakers. (4) In the adult heart, myocardial cells appear to be completely quiescent until stimulated by an extrinsic source. Under normal circumstances, this stimulus source is a pacemaker cell (or cells) of the S-A node, or some other part of the conduction system.

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