Ultrastructure of the Atrial, Ventricular, and Purkinje Cell, with Special Reference to the Genesis of Arrhythmias

By Marianne J. Legato, M.D.

SUMMARY
An examination of the anatomy of the atrial, ventricular, and Purkinje cells reveals that the internal composition of all cardiac myofibers is qualitatively the same: all have a single nucleus, sarcomeric and mitochondrial units, and a well-developed sarcoplasmic reticulum. There are important differences, however, in the extent and distribution of the cell membrane and its derivatives in the myofiber. The presence or absence of a transverse tubular system and the variation in the number and type of intercellular linkages explain at least some of the characteristic electrical and functional properties of individual types of cells. The overall pattern of cellular organization in working atrial, ventricular, and conducting tissue is reviewed, and possible anatomic bases for current theories of normal and abnormal impulse generation and conduction in the heart are discussed.

Additional Indexing Words:
Atrial cell Ventricular cell Purkinje cell Intercalated disc Transverse tubular system Sarcolemma

NORMAL CARDIAC beating depends on the coordinated activity of four principal cell types in the myocardium: first, the primitive cells of the sinoatrial node, which are postulated to initiate the heart's rhythm; secondly, the Purkinje cell, the principal component of the specialized conducting pathways over which the pacing impulse is rapidly and preferentially propagated; and third and fourth, the ordinary working cells of the atrium and the ventricle, which have primarily a contractile function and perform mechanical work. Knowledge of the important anatomic and physiologic differences between these cell types is essential to a better understanding both of how normal rhythm is generated and maintained and how abnormal rhythms arise and are perpetuated in the heart.

Although the principal roles of pacing and/or conducting cells and the working cardiac cells are quite different, many of their ultrastructural features are identical. In addition to a single nucleus, all myofibers contain orderly rows of sarcomeres, the contractile units of the cell; all have mitochondria which generate the energy for cell work; and all have a sarcoplasmic reticulum whose activity is responsible for cell relaxation. It is principally in the nature and distribution of the cell membrane and its derivatives that the two groups differ, and it is these differences which are relevant to the genesis of normal and abnormal rhythms and impulse conduction. We will, therefore, after describing the important anatomic characteristics of the four types of myofibers, consider in detail the sarcolemma and its two derivatives, the one wholly intracellular (the transverse tubular system) and the other the link between cells, the intercalated disc.

The Myofiber: Ultrastructural Characteristics
The "P" Cell
Thomas James has described a population of cells in both the sinus4 and the A-V nodes,2 which have a distinctive and rather primitive appearance. It is probable, although not certain, that these cells are the pacemaking units of the sinus node. They are round or elliptical, do not branch, and are characterized by the relative absence of electron-dense material in the cytoplasm. Apart from a large, eccentrically placed nucleus, they contain only infrequent, small mitochondria and a sparse population of randomly aligned myofibrils which are only a few sarcomeres in length. Because of the empty appearance of their sarcoplasm in comparison to the other cells of the heart, James calls these "pale" or "P" cells. He pointed out both the paucity

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Supported by a grant from the New York Heart Association. Dr. Legato is the recipient of a Research Career Development Award from the National Heart and Lung Institute of the National Institutes of Health.
and simplicity of intercellular connections between P cells and remarked on the fact that in most cases the cell membranes seem simply to make infrequent physical contact over very short areas; there are no intercalated discs or other types of ultrastructurally specialized linkages between these cells. Presumably, the infrequency of intercellular connections in this tissue can be correlated with the slow speed of conduction of an impulse through the sinus node.

**Atrial Cell**

The ordinary working cell of the human atrium is oval in shape and, in general, does not branch (fig. 1). It measures about 6–8 μ in diameter and is approximately 20–30 μ long. The interior of the cell, like the working ventricular myofiber, is packed with orderly rows of sarcomeric units, between which are interposed the elliptical mitochondria with their complex system of folded membranes or cristae upon which the energy-producing reactions of the cell occur.

Unlike the ventricular cell, the majority of atrial cells do not have the system of sarcomembran invaginations which extend downward from the cell surface into and throughout the substance of the myofiber and are known collectively as the transverse tubular system. The absence of a T system decreases the amount of surface membrane in the cell in comparison, for example, to the working ventricular myofiber.

The system of intercellular connections in atrial tissue is quite unique and differs from that in any other portion of the myocardium. Atrial muscle is made up of ribbons or bundles of two or three cells which lie very closely approximated along their lateral edges. The sarcolemmas of adjacent myofibers, separated by a gap which at its widest point is often only 0.2–0.3 μ, follow a parallel, undulating course over most of their margins. The gap between the cells progressively narrows until the adjacent sarcolemmae form, in a series of desmosomal and nexal junctions, a type of short, almost linear, and totally horizontally oriented intercalated disc, which is unique to atrial cells (fig. 1). There are also occasional short, end-to-end junctions between these myofibers which resemble the more usual type of intercalated disc found in ventricular myofibers in that they are perpendicularly oriented to the long axis of the cell and have a stepwise, rather than a straight overall configuration. These are less frequent than the horizontally oriented intercellular junctions. The intercellular spaces between the cell bundles are filled with collagen, which is strikingly abundant in the atria and in which is embedded the network of nerves and capillaries which supplies the tissue.

The pattern of intercellular connections in atrial tissue allows for impulse transmission through both end-to-end and side-to-side connections between cells. It would seem, therefore, that there is more opportunity in atrial than in ventricular tissue for disorganized patterns of impulse transmission and for reentrant stimulation, the summation of impulses and depressed conduction through one or more of the intercellular pathways. This diversity and relative abundance of contact between the surface areas of adjacent cells may help to explain the persistence for many years of a disorganized rhythm like fibrillation in atrial tissue.

**The Ventricular Cell**

The ventricular cell is the longest of all those in the heart, and on occasion reaches lengths of 100 μ. In contrast, its average diameter (10–15 μ) is intermediate between that of the smaller atrial cell and the wider Purkinje myofiber.

The entire organization of tissue and the system of intercellular linkages differs from those in the atrium. Ventricular myofibers are closely packed in an arrangement of broad sheets of branching cells joined, not side-to-side, but most frequently end-to-end by specialized intercellular junctions, the intercalated discs. The discs in this tissue have a characteristic stepwise configuration: the long, intermediate portions, in which there is no connection between sarcolemmas, lie along the long axis of the adjacent cells, while the majority of desmosomal and nexal junctions which form the specialized segment of the disc are oriented perpendicularly to the myofiber, at right angles to the unspecialized areas of the junction (fig. 2).

The bulk of the ventricular cell is filled with alternating rows of sarcomeres and mitochondria. There is a well-developed transverse tubular system, so abundant that there is a portion of a T tubule for each sarcomere. At the level of the sarcomere the T tubule comes into intimate apposition with the specialized cufflike modifications of the sarcoplasmic reticulum called "lateral sacs" to form the characteristic so-called "triads" and "diads." These consist of a central large round T-tubular vesicle flanked on one or both sides by the narrow, crescent-shaped cuff of the sarcoplasmic reticulum. If two lateral sacs are present and
Portions of four atrial cells, two of which are joined in the side-to-side linkage characteristic of this tissue (arrows). The extracellular compartment (ECS) contains collagen (C). Within the cell is a central nucleus (N) near which are atrial granules (AG) and rows of sarcomeric units (S). Mitochondria (M) are abundant. (Magnification × 7400.)

parenthesize the central T vesicle, the resulting configuration is called a triad; if the central T vesicle has only one lateral sac, the arrangement is called a diad.
Figure 2

Electron micrograph showing the stepwise course of the typical intercalated disc joining ventricular cells. Note the long unspecialized portion of the disc parallel to the long axis of the cell and the perpendicularly oriented much shorter specialized areas (arrows) of the disc. The frequent branching of the cells, which are filled with orderly rows of sarcomeres (S) and mitochondria (M), is characteristic of this tissue. Note the triadic and diadic units (circles). (Magnification × 9600.) (Inset) A triad, composed of a transverse tubular vesicle (T) flanked by two lateral sacs (LS). (Magnification × 62,000.)
The Ventricular Purkinje Cell and the Specialized Conducting Atrial Cell

There is good evidence that there are specialized, rapidly conducting, and extranodal cells which exist not only in the discrete bands of the conducting system in the subendocardial layer of the ventricular chambers, but in atrial tissue as well.

Purkinje cells, the specialized, rapidly conducting, myofibers of ventricular muscle, have been well described. They are 70–80 μ in diameter and are the broadest cells in the heart—one of the reasons that they are the most rapidly conducting of all myofibers.

The Purkinje cells have an abundance of linearly arranged sarcomeres (called myofibrils) and, contrary to a widely held and often-repeated dictum,

Table 1

<table>
<thead>
<tr>
<th>Related ultrastructural features</th>
<th>Purkinje cell</th>
<th>Ventricular cell</th>
<th>Related ultrastructural details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduction velocity =</td>
<td>4 m/sec</td>
<td>1 m/sec</td>
<td>Purkinje cell diameter: 7–80 μ</td>
</tr>
<tr>
<td>$K \times \text{radius of cell}$</td>
<td></td>
<td></td>
<td>Ventricular cell diameter: 10–15 μ</td>
</tr>
<tr>
<td>$C_m \times R_m$</td>
<td></td>
<td></td>
<td>Purkinje cell has much more extensive intercalated disc than the ventricular cell</td>
</tr>
<tr>
<td>Membrane capacitance $(C_m)$</td>
<td>1.28 μfaradays/cm²</td>
<td>0.81 μfaradays/cm²</td>
<td>Ventricular cells have an extensive T system and a much less extensive intercalated disc; either may be related to higher $R_m$ in ventricular cells</td>
</tr>
<tr>
<td>Membrane resistance $(R_m)$</td>
<td>1220–1700 ohms/cm²</td>
<td>9100 ohms/cm²</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

Comparison of Ultrastructural Features of Atrial, Ventricular, and Purkinje Cells: Summary

<table>
<thead>
<tr>
<th>Feature</th>
<th>Atrial</th>
<th>Ventricular</th>
<th>Purkinje</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimension and shape</td>
<td>Elliptical, 6–8μ wide X 20μ long</td>
<td>Narrow (15–20μ wide) and long (100μ); frequent branching</td>
<td>Broad (80μ in diameter)</td>
</tr>
<tr>
<td>Cell contents:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myofibrils</td>
<td>Fundamentally identical organization in long parallel rows</td>
<td>Most abundant</td>
<td>Less abundant than in ventricular cell</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Less abundant than in ventricular cell</td>
<td></td>
<td>Characteristic large pools both intermyofibrillar and subsarcolemmal</td>
</tr>
<tr>
<td>Glycogen</td>
<td>Present between myofibrils with mitochondria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granules</td>
<td>“Atrial granules”: function and composition unknown</td>
<td>“Residual bodies” high in catecholamine content</td>
<td></td>
</tr>
<tr>
<td>Transverse tubular system</td>
<td>Absent</td>
<td>Abundant</td>
<td>Absent</td>
</tr>
<tr>
<td>Sarcolemmic reticulum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercellular linkages:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercalated discs</td>
<td>Short, horizontally oriented to long axis of cell; less frequent, short perpendicularly oriented discs</td>
<td>Characteristic stepwise configuration with nonspecialized portions horizontal to long axis of myofiber and specialized areas perpendicular to long axis of myofiber: principally end-to-end links between cells</td>
<td>Oblique and zigzag course; highest proportion of specialized linkages with greatest surface area of all three cell types</td>
</tr>
<tr>
<td>Side-to-side connections</td>
<td>Principal location of cell-to-cell connections</td>
<td>Brief; infrequent</td>
<td>Abundant</td>
</tr>
</tbody>
</table>

Circulation, Volume XLVII, January 1973
they are by no means all concentrated in the periphery of the cell, but fill it in a rather homogeneous pattern similar to that of the working ventricular cell. The myofibrillar arrangement is interrupted in certain areas by large, relatively clear pools of sarcoplasm filled with glycogen particles, mitochondria, and sarcoplasmic reticular tubules (fig. 3). Such areas of increased glycogen concentration are also prominent in the subsarcolemmal areas, where they cause large outpocketings of the cell membrane and give an undulating, smooth contour to the cell. The internal resistance of the Purkinje cell is one third that of the ventricular cell, and it may be that these large areas of the cell filled not with contractile units but with relatively clear pools of glycogen in sarcoplasm explain this low internal resistance.

The Purkinje cell has no T-tubular system. There is only an occasional triad or diad in the transitional cells between Purkinje and working ventricular myocardium. Fozzard’s observation that the Purkinje cell membrane capacitance is greater than that of ventricular fibers is puzzling in the face of this absence of a transverse tubular system. The tremendous surface area provided by the intercalated disc, however, which in Purkinje tissue is very extensive and complex, is a likely reason for the high capacitance value of Purkinje tissue.

The frequent finding of three Purkinje cells connected in a Y-shaped arrangement (fig. 3, bottom) is relevant to the theories of Cranefield and Hoffman concerning the role of undirectional block, and summation and inhibition of impulses in the genesis of reentrant rhythm. They have postulated the necessity of such a configuration in explaining the mechanisms of arrhythmias arising in the Purkinje network, and it is of interest to see that it does indeed exist at the cellular level.

There are areas of Purkinje tissue with a mosaic-like arrangement of cells. Adjacent sarcolemmal membranes, although they do not form specialized desmosomal or nexal junctions, are no further than 300–400 Å apart along extensive portions of their surfaces in such sections of the myocardium. This type of cellular organization is frequent in Purkinje tissue and may be a factor in the rapid speed of conduction in these fibers, as is, no doubt, the complex and extensive intercalated disc joining Purkinje cells (fig. 3, top).

Berger has described a population of atrial cells in the rat which are found in the subendocardial muscle layer, and which have many of the characteristics of the Purkinje cells of the ventricle. He postulates that these may be the type of cell which makes up the tissue responsible for rapid and specialized conduction in the atrial myocardium and, although this has not been proven by correlative electrophysiologic evidence, there is a good morphologic basis on which to base this assumption.

The Cell Membrane and its Derivatives: The Transverse Tubular System and the Intercalated Disc

The Sarcolemma

The cardiac cell membrane, or sarcolemma, is a chemically and structurally complex barrier between the contents of the myofiber and the extracellular space. By virtue of its selective permeability to charged particles, it maintains an asymmetry in ionic concentration between the interior and exterior of the cell. Excitation is mediated by a series of rapidly and highly organized variations in sarcolemmal permeability to various types of ionic species (both positively and negatively charged) which are time and voltage dependent. These changes produce sequential alterations in the electrical potential across the cell membrane known collectively as the action potential.

Atrial, ventricular, and Purkinje cells all have well-defined, different, and characteristic action potentials. It is probable, therefore, that the ionic permeability characteristics of their sarcolemmata vary, at least quantitatively, at any given time in the sequence of the generation of the action potential, and evidence has recently been offered to show that this is indeed the case. This further implies differences in sarcolemmal composition and architecture. The nature of these differences is, at the moment, completely obscure; and we cannot explain either on an ultrastructural or biochemical basis the observed differences in action potentials between the various kinds of myocardial cells. Indeed, our knowledge is very incomplete regarding which specific ions and in what concentrations these ions are carried across the cell membrane during excitation and the return to the resting state.

The sarcolemma of all myocardial cells has two layers in electron micrographs; a thin, electron-dense plasma membrane and a much thicker outer layer of amorphous material that coats the outermost aspect of the myofiber, the perimembrane or basement membrane (fig. 4, top).

The plasma membrane has the basic structure of the unit membrane and is built around an inner
core of a bipolar lipid layer, oriented so that the nonpolar, carbon chains are directed interiorly. The outer, polar segments of the lipid molecules serve as attachment sites for the two nonlipid monolayers which form the inner and outermost membrane leaflets. It is important to realize that the latter are not the same, and that the sarcolemma has a different inner and outer surface. This explains such phenomena as the asymmetry of the sodium pump, which is localized to the sarcolemma, and which is
stimulated either by a high intracellular concentration of sodium or a high external concentration of potassium. The plasma membrane is trilayered; its appearance in electron micrographs, which is that of a single, dark line, is due to the fact that unless special technics are used the outermost layer does not stain, and that the middle, lipid portion of the membrane is not electron dense. What we see, then, is only the monolayer which makes up the innermost surface of the sarcolemma.

The perimembrane (or basement membrane) is rich in carbohydrates, probably in large part a glycoprotein, with weakly acid residues capable of binding cations.9 Recent data10 have been offered to indicate that the sarcolemma, and probably the perimembrane, with its ability to bind cations, is the most likely source of beat-to-beat calcium entry into the cell at the moment of depolarization. It is this calcium which is presented to the area of the sarcomeric myofilaments where, prompting the formation of cross bridges between actin and myosin, it engenders the contractile event. Cardiac muscle has an extraordinary dependence on external calcium concentration for the generation of systolic force; lanthanum, which causes complete uncoupling of the cardiac cell,10 binds exclusively to the sarcolemma. This observation supports the concept of a superficial site for excitation-contraction coupling calcium in the heart.

The Transverse Tubular System: Origin, Anatomy and Function

The origin of the transverse tubular system, a derivative of the sarcolemma whose lumen is filled with perimembrane and lined with plasma membrane, has prompted three important assumptions among cardiac physiologists which are either being modified or wholly rejected as new data accumulate.

First, since the cell membrane at the surface of the cell is contiguous with that of the transverse tubule, it was generally felt that the ionic permeabilities of both were identical and that the depolarizing impulse was propagated in exactly the same manner over the sarcolemma and the membrane of the transverse tubular system. Second, it was held that the extracellular compartment, which is not restricted to the surface of the cell with a T system but extends downward to all levels of the myofiber via the T-tubular lumen, was of the same composition in the transverse tubular system as it was at the cell surface. Third, the proximity of the T tubules to the calcium storage depots of the lateral sacs of the sarcoplasmic reticulum prompted the assumption that excitation, mediated throughout the myofiber over the T system, caused the release of calcium ion from the lateral sacs to the area of the myofilaments, thus engendering contraction. The diadic and triadic units of the ventricular myofiber, therefore, were postulated to be the anatomic substrate for excitation-contraction coupling in the cell.

It may be that neither the perimembrane nor the plasma membrane of the transverse tubular system, although in direct continuity with the sarcolemma, is identical with the cell membrane at the surface of the myofiber. The lumen of the transverse tubules in the rat, for example, shows nucleoside monophosphatase activity, which the perimembrane at the surface of the cell does not.11 Howse has shown that rhenium red, which stains the sarcolemma, does not stain the plasma membrane that lines the transverse tubular system.9

It is demonstrated that the ionic permeabilities of the T system are not identical with those of the sarcolemma. With respect to the movement of ions between the T-tubular lumen and the extracellular space at the cell surface, the perimembrane does not allow unmodified and unrestricted diffusion of either charged or uncharged particles throughout the system, so that the composition of the extracellular compartment in the body of the myofiber may not be identical to that at the surface of the cell. Chloride deprivation, for example, causes selective dilatation of the transverse tubular lumen in both skeletal12 and cardiac13 muscle.

The observation that neither Purkinje cells nor, almost without exception, atrial cells, have a

Figure 3

(Top) The mosaic appearance of some portions of Purkinje tissue is seen in this photograph of three cells (1,2,3) in close apposition over most of their surface areas. Note the extensive area of the intercalated disc joining the cells. ECS = extracellular space. (Magnification X 5000.) (Bottom) Three Purkinje cells (1,2,3) joined at an intercalated disc (arrows) in one of the Y-shaped configurations often seen in both Purkinje and ventricular tissue. Cranefield and Hoffman postulate the existence of such an arrangement in their concept of the mechanism of reentrant rhythms (see text). (Magnification X 6000.)

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transverse tubular system makes it quite clear that excitation-contraction coupling occurs without the T tubule and diadic or triadic units. Further, it is now apparent that the working ventricular cell itself acquires a transverse tubular system sometime in postnatal life in several mammalian species.\textsuperscript{14, 15} long after it has been rhythmically and rapidly beating.

The function of the transverse tubular system is unknown; further, the reason for its close approximation to the calcium storage depots of the lateral sacs is not apparent. The T system apparently does
not make a great contribution to membrane capacitance ($C_m$), since the $C_m$ of the Purkinje fiber is measured at 1.28 μfaraday/cm² in comparison to that of 0.81 μfaraday/cm² in the ventricular working cell. While destruction of the T system in skeletal muscle completely suppresses contraction in response to the action potential,17 the cardiac cell is resistant to disruption18 by glycerol-hypertonic Ringers. Apparently there are important differences between the T systems of cardiac and skeletal muscle.

It is interesting to make the observation that ventricular cells grown in tissue culture, at the time that they are beating in a coordinated fashion and thus are obviously capable of spontaneous depolarization, do not have a transverse tubular system. In contrast, the adult ventricular myofiber has no specialized pacemaking ability, and one might speculate that with the development of a transverse tubular system (which occurs, at least in some species, in postnatal life) the ability of phase 4 spontaneous depolarization is lost. This, like all other current thoughts about the function of the T system, requires further investigation.

The Intercellular Junction

The intercalated disc, the intricate and highly specialized sarcolemmal derivative joining cells in the heart, is unique to cardiac tissue. It has three specialized types of intercellular connections: the fascia adherens, the desmosome, and the nexus.

The fascia adherentes are the portions of the disc into which the thin filaments of the terminal sarcomeres of the cell insert. They have no role in impulse transmission between cells, but serve only to supply the anchoring Z substance for myofilaments.

The desmosome (fig. 4, middle) is a multilayered connection between cells at which the intercellular gap measures only 200 A. The work of Rayns and Simpson19 shows that the material in the gap has a highly ordered ultrastructure.

The nexus (fig. 4, bottom) is the intercellular link in which the sarcolemmata of adjacent cells come together with apparent physical approximation of their outer leaflets. McNutt has pointed out that, depending on the stain and the preservative used, the nexus may have at least three different appearances,20 but he emphasizes the fact that in properly prepared sections the outer membrane leaflets are not fused, but separated by a 20–30 A gap. Freeze etch techniques, which entail fracture of the tissue through nexal junctions,21 and experiments using lanthanum as an extracellular marker22 show that the intermembranous gap of the nexus, like that of the desmosome, has a very specialized ultrastructure. There are hexagonally organized subunits connecting the two-cell membranes in this type of junction which may be channels for the transmission of excitation between cells.

Weidman has convincingly demonstrated that the intercalated disc is functionally a low-resistance junction.23 However, whether the desmosomal or the nexal portions of the disc (or both) are the sites of electrical transmission of the exciting impulse from cell to cell is unknown. Certainly the nature of the two junctions is different; for example, calcium is required to maintain the stability of desmosomal, but not nexal linkages.24 As Kawamura pointed out in his review25 there has been no experiment which exclusively damaged the nexal link between cells, leaving all other junctions intact. Direct evidence that this junction is the point of transmission of intercellular impulses is, therefore, lacking.

Against the concept of the nexal junctions being the sole site of the low-resistance connection between cells is the fact that in tissue culture preparations of rat ventricular cells sheets of primitive myoblasts beat in unison.26 Yet, there are no nexal junctions at this stage in development (2–6

Figure 4

(Top) The scalloped contour of the sarcolemma in ventricular cells, which forms arches over each sarcomere and dips down at the Z band, is evident in this micrograph of a portion of a ventricular cell. The two components of the sarcolemma are clearly seen: the electron-dense layer of the plasma membrane (P) and the thicker, amorphous outer layer of the perimembrane (PM) or basement membrane. ECS = extracellular space. (Magnification × 33,000.) (Middle) The desmosome (D) shown here is a highly ordered multilayered specialized junction between cells which may be an electrically low-resistance connection over which impulse transmission is effected in the tissue. (Magnification × 175,000.) (Bottom) The nexus (N) appears here as a five-layered complex with a central dark line. The central line does not represent fusion of the outer leaflets of the adjacent sarcolemmas; there is a 20–30 A gap between the cell membranes (see text). This appearance is an artifact of tissue preparation but is the one most frequently seen in electron micrographs of cardiac muscle. (Magnification × 135,000.)
days); only desmosomal links exist between the cells. There are types of cells between which no nexal junctions have been observed. James describes none between the P cells of the sinus node. Baldwin, who electrically uncoupled frog atrial cells by mechanical injury, observed that the nexal or “close junctions” between cells were undisturbed after such a procedure.

From these observations, it is evident that there are cardiac cells which beat in unison with few or no nexal junctions, and there are others that are electrically uncoupled by maneuvers which leave the nexal junction undisturbed. It may be the desmosome or even a close but unspecialized gap between cells which simply involves intermingling of adjacent perimembranes which are the sites of transmission of impulses from cell to cell.

There are lateral sacs of the sarcoplasmic reticulum, as we have described in this laboratory, along the entire course of the transverse tubular membrane which are depots for relatively large concentrations of calcium ion. There are also lateral sacs under the sarcolemma and along the nonspecialized portions of the intercalated disc; such peripheral coupling sites, as they are sometimes called, are universally present in cardiac cells, even 2-day-old myoblasts grown in tissue culture. Calcium is of primary importance in controlling membrane permeability; Lowenstein points out that when calcium concentration (which is normally low on both sides of junctional membranes) is raised to a concentration above $10^{-4}$ M, each cell seals off as a unit and no transmission occurs. It is conceivable that the lateral sacs at the periphery of the cell (whether along the intercalated disc, the unmodified sarcolemma at the cell surface, or the transverse tubular system) by regulating the calcium concentration at the interior of the cell membrane, may determine the permeability characteristics and electrical resistance of all the membrane systems involved in excitation and the intercellular transmission of impulses. The role of the lateral sacs of the sarcoplasmic reticulum needs much more clarification.

Since we do not know what kind of intercellular link is the one required for cell-to-cell transmission, it is not possible to relate the speed of conduction in any type of cardiac tissue to the number and kind of specialized intercellular junctions. It seems probable that the fewer and more simple the intercellular junctions, the slower the conduction through the tissue. Thus James reasons that the slow speed of impulse transmission through the sinus node is due to the paucity of connections between P cells. It is also probably relevant that the intercalated discs of Purkinje cells, which are the most rapidly conducting tissue in the heart, have very few unspecialized areas in their intercalated discs; in contrast, the ventricular cell has long unspecialized areas in its stepwise disc, with only the short, perpendicularly oriented portions containing nexal and desmosomal links. Atrial cells, which are probably slower in speed of conduction than either Purkinje or ventricular cells, have shorter intercalated discs than the other two types of cells, and a relatively smaller part of the cell membrane is involved in specialized intercellular junctions.

In summary, cardiac tissue is morphologically heterogeneous. The electrical properties of the myofiber, the overall pattern of cellular organization, the type and extent of intercellular linkages, and the systems of sarcolemmal derivatives in atrial, ventricular, and Purkinje tissue all differ; it is these differences which are essential to the generation and maintenance of normal rhythm and conduction in the heart. As our knowledge of ultrastructural detail increases, we can postulate the anatomic bases for the emergence of ectopic pacemakers, the potential pathways for the initiation and perpetuation of aberrant conduction through the tissue, and the structural reasons for the tendency of some abnormal rhythms to persist, while others are very transient. A detailed knowledge of the ultrastructure of the myofiber is more and more information which contributes significantly to our understanding of both normal and aberrant cardiac function.

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Circulation, Volume XLVII, January 1973
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Genesis of Arrhythmias
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Circulation. 1973;47:178-189
doi: 10.1161/01.CIR.47.1.178

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Corrections

Legato MJ: Circulation 47: 178, 1973. On page 182, in table 1, and on page 187, line 3, capacitance of the Purkinje cell is shown as 1.28 μfarads/cm²; it should read “12.8 μfarads/cm².”

James TN: Circulation 47: 362, 1973. The author wishes to acknowledge that the fifth annual George C. Griffith lecture, published in February, was sponsored and indeed made possible exclusively by the generous support of the Los Angeles County Heart Association.