THE scholarly reviews on new aspects of the mechanisms underlying irregular heart action presented in this symposium would have been considered by many to be "nonrelevant" and esoteric if published a few years ago. To some, however, it was quite obvious at that time that a morphologic and physiologic correlation of cardiac function was imminent and that this in turn would lead to a better and more useful practical concept of irregular heart action. The usual separation of electrocardiographic analyses into those concerned with the interpretation of the form of an electrocardiographic complex, and into others concerned solely with the sequence of beats has largely disappeared today. At best this habit was a didactic device based only on descriptive and empirical observations. When several old physiologic concepts of cardiac function were reinvestigated these arbitrary divisions became obsolete.

All alterations of an electrocardiographic record, whether the sequence of beats is regular or not, are ultimately dependent on changes in the spread of electrical activity from one fiber to the next. This involves changes in several fundamental parameters of cardiac function which occur on the cellular and subcellular level: (a) changes in the duration of the excitatory process of a fiber, which has a direct bearing on the ability of tissues to respond to successive stimuli ("refractoriness"); (b) changes in the rate of excitation, which expresses the ability of a fiber to change from its resting to its excitatory state ("depolarization"), and which, in turn, is a function of the rapidity of the electrochemical processes occurring within and on the cellular membranes; and (c) the time course of the recovery of a fiber to its original resting condition ("repolarization"). In essence, these factors control the speed and direction by which the electrical changes are transmitted from one fiber to the next, and they determine the rate at which an individual fiber is able to respond fully or partially to a premature stimulus.

An additional factor deals with (d) the ability of probably all cardiac fibers for "self-depolarization," i.e., for a cell to change the level of its resting potential and eventually reach a voltage threshold where the cell undergoes spontaneous excitation ("automaticity"). This spontaneous diastolic depolarization is a characteristic of all pacemaker sites but under pathologic circumstances may be induced in other fibers not considered as primary loci of impulse formation. The readiness for spontaneous discharge depends on additional modifications of the ionic current flowing through the cell membrane. It suffices to say that

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these concepts have now been verified abundantly by the use of the microelectrode technique which allows an insight into the ionic mechanisms underlying the physiologic state of excitation. The study of irregular heart action has been greatly advanced by this technique.

The interplay of these parameters influences not only the appearance of the form of a cellular action potential, but also the configuration of a surface electrocardiogram and vectorcardiogram, since the passive properties of conduction of a current through the tissues of the thorax play only a minor role in shaping the final clinical record. It also determines the conduction velocity and the path to be taken by the wave front of excitation, i.e., the spread of the "action current" (sequential changes of fibers from the resting to the active state). Lastly, these electrophysiologic parameters are responsible for changes in the sequence of beats because they control the homogeneity of refractoriness: to the degree by which fibers differ in the duration of their action potential they will respond differently to successive stimuli. This dispersion of responsiveness underlies such mechanisms as reentry, atrial and ventricular echoes, conduction over accessory pathways, and disturbances in atrioventricular and intraventricular conduction, and is at the root of the chaotic excitatory wavelets of fibrillation. The appearance of abnormal electrocardiographic complexes in regular rhythms is also dependent on these same electrophysiologic parameters.

It is interesting that the first original papers on transcellular membrane potentials of the heart contain the essential ingredients for a logical approach to a rhythm analysis. In the paper by Woodbury, Hecht, and Christopheron, the temperature-dependent changes of the recovery process of frog ventricular muscle fibers were recognized as independent variables and were termed phases 1, 2, and 3 of the recovery process. They were thought to have some influence on the shape of the surface electrocardiogram and to determine the refractoriness of ventricular tissue. In the classical paper by Draper and Weidmann on sheep Purkinje fibers, conduction velocity was shown to be a function of the magnitude of the resting potential, and the gradual diastolic depolarization, the hallmark of pacemaker tissues, was clearly described there. Later refinements of microelectrode techniques have allowed a remarkably sophisticated insight into the active (i.e., metabolically driven) and passive properties of excitable tissues and have pointed to the differences and similarities which exist between nerve fibers, skeletal, cardiac, and smooth muscle.

The insertion into a single cardiac fiber of two or more electrodes to measure and to control simultaneously both voltage and current flow has clarified the interplay of ionic exchanges in heart muscle which in turn are controlled by physicochemical alterations in the structure of cellular membranes. The technique of multiple impalments allowed the calculation of fundamental electrical constants of several types of cardiac fibers. These determinations proved to be of great interest for a proper understanding of intrinsic pacemaker function, intracardiac conduction from fiber to fiber, and the role of ions in mechanism and control of irregular heart action. A special form of multiple impalement with microelectrodes uses "voltage clamping," a technique adapted from the neurophysiologists. By means of a feedback amplifier it controls the intracardiac voltage at any given level and records the resulting current flow through the membrane at that moment and throughout the preparation. If the preparation is small enough and uninjured, the internal current density thus measured is equal throughout the impaled fiber. Transmembrane flow, the prime factor of an electrocardiographic curve, can thus be recorded and measured directly under various conditions and at various stages of depolarization, polarization reversal, and hyperpolarization. One can program a set of voltage clamp conditions which simulates any part or all of the voltage-time changes of an action potential and obtain a record of the current flowing through the cellular membrane at any time during excitation and recovery. A further
extension of voltage clamp techniques involves the simultaneous recording of mechanical contraction of the impaled fiber together with controlled voltage levels or voltage and current flow records. Thus one can explore directly the link between excitation and contraction. This probably, at present, represents the ultimate in technical refinements in this area.  

These developments in basic understanding of cardiac function seemed at times to have outstripped the anatomical considerations. The morphologic aspects of cardiac function, however, also have entered an accelerated phase. The detailed knowledge of the histology and ultrastructure of the normal heart had remained remarkably incomplete until a few years ago. At a meeting where sophisticated cardiac voltage clamping was first reported by two independent groups of investigators, the papers on histologic and electron microscopic features of cardiac tissues stressed many areas of morphologic uncertainties. In this light, some of the confident statements linking certain electron microscopic findings with specific disease states must be accepted with reservations. However, the integration of the morphologic approach with clinical and electrophysiologic observations begins to yield a rich, if in some aspects still incomplete, harvest. The extensive clinical, physiologic, and morphologic studies by Trautwein and Uchizono on the sinus node, those by T. James on intraatrial and ativoventricular conduction pathways, the histologic studies by M. Lev, and the comparative aspects of the cardiac conduction system by Trux, to name only a few investigators, have led to some clarification on details of structure as the basis for excitation and for the normal and abnormal impulse propagation. The demonstrations of various specific atrial tracks, bypass fibers, and anomalous ativoventricular connections are of interest. Proof is still required that these special fibers are involved in electrical propagation of an impulse. In atrial tissues some areas show striking differences in shape and duration of the action potential when compared to other atrial regions. Such differences must influence intraatrial impulse conduction. The rich supply of vesiculated (vagal) or granulated (adrenergic) nerve endings in atrial tissue is also likely to influence the electrophysiologic properties and constants of one atrial region as contrasted to another. This contributes to an unstable atrial sequence of conduction. On the other hand, the dissection of an anatomical connection does not provide proof that these strands are involved in a preferential pathway for the conduction of an impulse.

On a more fundamental level the electron microscope has provided information on the detailed structure of the transcellular membrane of heart muscle. Among other observations, two very important morphologic-functional interrelationships were established: (1) the ultrastructural basis for low electrical resistance pathways from cell to cell necessary for intracellular axoplasmic current spread was conclusively demonstrated (diads and tight junctions); (2) a logical answer to the apparent differences in electrical constants, particularly capacitance of heart muscle as compared to nerve, has been provided by a demonstration of not only the intracellular canal systems and infoldings of the surface membrane, but also by the discovery of finger-like membrane projections and interlocking pivots through the extent of the total membrane surface. The cardiac membrane is therefore a complexly folded, interdigitating cover over and around the cardiac axoplasm (the seat of the contractile mechanisms) with which it intimately interacts.

During the last few years these fundamental studies concerned with details of cellular and subcellular morphology and physiology as a basis of irregular heart action have been complemented by observations in experimental electrocardiography of a more conventional type, which, in their approach, may be considered an extension of F. N. Wilson's concepts developed between 1930 and 1950. These new studies concern themselves with the spread of excitation from atrial to ventricular musculature and with the intraventricular conduction system. Earlier studies
on details in intramural spread of excitation by Scher, Durrer, Sodi, Pallares, and Prinzmetal, and studies on the excitation of endocardial surfaces by intracavitary electrocardiography, while not of immediate concern to the problem of cardiac irregularities, provide the bridge between older observations and newer concepts.

Two specific areas of clinical and experimental study are particularly pertinent:

1. Atrioventricular conduction over the junctional region which embraces the approach fibers to the atrioventricular node, the atrioventricular node itself, and the nonbranching portion of the atrioventricular bundle, have been studied in detail by several groups using endocardial electrodes in close proximity to the atrioventricular bundle. The arrival of an impulse at this electrode position signals excitation of a portion of the junctional region, presumably the upper, nonbranching portion of the atrioventricular bundle. Such spikes were overlooked in earlier human endocardial electrocardiograms but were clearly described by Giraud et al.,11 and by Watson, Emslie-Smith, and Lowe.12 Such records allow the separation of the junctional region into an upper, atrial portion under autonomic control, and a lower ventricular portion of the His bundle system which is essentially autonomous. In consequence, the P-R interval of the electrocardiogram is divided into a P-H (atrial-to-His) and H-R (or H-V—His-to-ventricle) part. Lesions in the junctional region can now be located with considerable precision, and various forms of incomplete and partial heart block as well as the site of a complete interruption of atrioventricular conduction can be pinpointed with considerable accuracy.13 There are practical therapeutic considerations associated with locating sites of block within the junctional region: in the absence of His bundle recording, the use of autonomic blocking agents and the behavior of A-V conduction following atrial pacing at various heart rates has proven to be an alternative, though not quite as precise, method for differentiating atrial from ventricular forms of A-V conduction block.

2. The branching portion of the atrioventricular bundle has been scrutinized experimentally and clinically by several methods and by several investigators. Based on these extensive and anatomic correlated observations, it has become feasible and quite popular to define blocks in the major rami or fascicles of the bundle branches and at least for the left bundle branch to assign certain electrocardiographic and vectorcardiographic configurations to predominant involvements of only the anterior or posterior portions of the branches. The diagnosis of biventricular involvement of these bundle branches, known to the pathologists for a long time, can now be made with fair (though not absolute) assurance. One combination, the presence of right bundle-branch block, with pronounced left axis deviation, first singled out as an entity by F. N. Wilson,14 can be confined to a lesion of the bifurcation or lesion in the right bundle and anterior fascicles of the left bundle. Marked right and left axis deviation of QRS without widening of the ventricular complexes are now in many cases considered examples of partial block or block of portions of the left bundle. With some skill and pencil and paper, one can now define various forms of partial, incomplete, and complete interruptions of the branching system of the conduction pathways occurring in succession or simultaneously at various sites. This important and exciting area of experimental and clinical electrophysiology received a new life with the recent appearance of M. Rosenbaum's monograph.15

Here are, then, a few reasons why the morphologic, experimental, and clinical area of the study of the irregular heart action, its mechanism, diagnosis, and therapy have of late become of renewed interest. Languishing in the shadows of a somewhat dull empiricism a few years ago, it has become a cardiological Cinderella—we are having a ball!

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