Clinical Disorders of the Heart Beat

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Preface

The object of this revised edition is to present recent developments and bring the subject of clinical disorders of the heart beat up-to-date. This subject has been the center of intensive activity in the past decade, in both the fields of clinical and basic research. Because of recent developments, arrhythmias have assumed a more important role in clinical medicine. This greater emphasis has resulted from the increased use of long-term monitoring devices, which have disclosed the presence of arrhythmias during various portions of the day; the marked degree of disability that can accompany arrhythmias; the development of additional antiarrhythmic agents, both for prophylaxis and active treatment; the prognostic importance of the presence of arrhythmias, particularly as a cause of sudden death; and the significant contribution of arrhythmias to the morbidity and mortality of patients during the acute stage of myocardial infarction in both the prehospital and the hospital phase.

Advances have been made in the development of diagnostic methods for the recognition and specific identification of various types of arrhythmias, such as the use of intracardiac electrocardiography, the His bundle electrogram, and Doppler ultrasound techniques. Long-term monitoring devices and the introduction of miniaturized equipment that can be carried by the subject during daily activities are invaluable aids in the diagnosis of various arrhythmias when the usual methods are unavailable.

The development of coronary care units has added materially to our knowledge of the incidence and significance of various arrhythmias and their therapeutic implications. The chapter dealing with myocardial infarction has been expanded to incorporate a section on sudden death.

Much new knowledge has been obtained on the electrophysiology and genesis of cardiac arrhythmias. This has entailed study of the monophasic action potentials of each of the different types of cells in the heart, and the study of the electrogram and the various structures involved with intracardiac conduction, particularly various portions of the A–V transmission system, using sophisticated techniques of histopathology, electron microscopy and electrophysiology. The more recent concepts of atrial flutter and fibrillation, paroxysmal junctional tachycardia are discussed. The various preexcitation syndromes are reviewed; the newer approaches to therapy, including the present status of the surgical interruption of the accessory pathway, are presented.

An attempt has been made to correlate the anatomic and electrophysiologic basis of the various arrhythmias with the clinical and hemodynamic manifestations together with a rational approach to therapy.

Although recent pharmacologic advances and techniques have resulted in the discovery of few clinically significant new drugs, the site of action, limitations in the use and the production of toxic effects of the well-known antiarrhythmic agents have been clarified. The older and more commonly used drugs—namely, sympathomimetic amines, sympathetic blocking agents, quinidine, procaine amide, and digitalis—have been reviewed in the light of these developments. A new section has been written for each of the few new drugs that have proved to be valuable (*e.g.*, lidocaine, diphenylhydantoin, and beta-blocking agents).

The chapter on pacemakers has been rewritten and updated. This includes the discussion of the different types of pulse generators (fixed rate, atrial-triggered, demand, and standby) and considerations involved in choosing a particular type for the individual patient. The indications for their use have been amplified to include bradyarrhythmias and other states predisposing to complete A–V heart block and syncopal episodes, as

well as their recent employment for controlling tachyarrhythmias.

An important problem in therapy is the relative indication for a specific therapeutic modality in a given situation; that is, which drug or electronic device has priority. By discussing such considerations in some detail, an attempt has been made to clarify these and similar problems. Where controversies exist, I have endeavored to discuss the various viewpoints and the present status of the problem.

The format has been revised, and the book has been divided into six sections: The introduction, Section 1, includes anatomic, physiologic and hemodynamic considerations; Section 2, the individual arrhythmias, their incidence, diagnosis, therapy and prognosis; Section 3, general diagnostic procedures; Section 4, the arrhythmias that might be encountered in various clinical states and during various diagnostic procedures; Section 5, chapters on the antiarrhythmic drugs which include a discussion of their pharmacologic effects, indications, administration, and toxicity; Section 6, the primary procedures in therapy other than drugs (*i.e.*, carotid sinus pressure, artificial pacemakers, defibrillation, and countershock).

Most of the chapters from the previous edition have been completely rewritten; others have been extensively revised and brought up-to-date. New figures have been added that illustrate the more current concepts, and the legends of previous figures have all been revised in the interest of clarity. The bibliography at the end of each chapter has been amplified to include important recent references relating to the various subjects discussed. Box-form summaries of salient features are included. The glossary has been amplified and revised.

In the preparation of this book, I have endeavored to keep in mind the interests of the medical student, the internist, and the cardiologist.

I particularly wish to thank Richard Devereux and Leonard N. Horowitz, for their tireless effort in gathering recent material and participating in the numerous revisions of various portions of the text. I wish to thank Alvin Heller and Paul Ginsberg for their cooperation in various stages of the preparation of the manuscript.

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Section 1 • Introduction

CHAPTER 1
Anatomy

GENERAL CONSIDERATIONS

Anatomic concepts have been revised in recent years, not only from the standpoint of "anatomy" per se, but as a result of studies in histology, electron microscopy, histochemistry, physiology, and pathology. The result of these new correlations has been a clearer understanding of the function of various anatomic structures; this has helped considerably in the study of the propagation of the normal cardiac impulse and the genesis of arrhythmias. Moreover, there is an intimate relationship between the anatomy, especially that of pacemaker cells and conduction fibers, and the etiology, mechanisms, and manifestations of cardiac arrhythmias. Because of their paramount importance to arrhythmias, we will consider primarily the pacemaker cells and the conduction system of the heart. Recent advances in the available methods of study have contributed immeasurably to our knowledge of these specialized cardiac tissues, although many problems are still unresolved.

The heart may be divided into (1) the undifferentiated myocardium, the principal function of which is to pump blood in response to the cardiac impulse; (2) the fibrous tissue, valves, and chorda tendineae, which control the flow of blood; and (3) those tissues of the heart specialized for impulse initiation and propagation (S–A node, atrial tracts, A–V junction, His-Purkinje system, and other specialized fibers). The undifferentiated myocardium forms the four chambers of the heart: (1) the two thin-walled atria, constituting part of the low-pressure system, which functions principally to receive, store, and transmit the blood returning from the systemic and pulmonary venous system; and (2) the two thick-walled ventricles, which function primarily to pump the blood under considerable pressure into the pulmonary artery and aorta, from which it is distributed.

HISTORY

Because of the importance of placing the present state of knowledge in perspective, the development of concepts concerning the specialized tissues of the heart particularly merit discussion.

The study of the pacemaker and the specialized conducting tissues of the heart began about 1845 with the demonstration of the terminal elements of the system, namely, the Purkinje fibers in the sheep heart.[100] The existence of a conduction system composed of specialized muscle fibers joining the atria and ventricle was first established by Gaskell's work with frogs and tortoises in 1882.[26] The bundle of His was the next component of the conduction system to be definitely identified[35] (1893). Kent had previously demonstrated what he thought were muscular connections between the atria and ventricles and he also dissected the atrioventricular (A–V) node (1892–1893).[65,66] However, he did not fully appraise its importance, and it has been suggested that the muscular elements demonstrated by him may actually be insertions of atrial musculature at the A–V groove and not connections between the atria and ventricles.[76] Fourteen years later, Tawara[121]

(1906) further delineated the structure of the A–V node. His main contribution was the demonstration that the A–V node, bundle of His, bundle branches, and Purkinje fibers were anatomically continuous structures. The sinoatrial (S–A) node, the dominant pacemaker of the heart, was identified the next year by Keith and Flack.[64] The specialized atrial tracts were the last major structure to be demonstrated.

Early workers[23,24,64,88,122,123,136] described what they considered to be special pathways connecting the S–A and A–V nodes, but the role of these structures in impulse transmission was challenged by Lewis,[81] who demonstrated uniform and even activation of the atrial musculature, indicating that transmission occurred through the muscle itself. Recently, however, Lev,[74] Truex,[127] Meredith and Titus,[89] and James[49,114] have demonstrated what they consider to be specific tracts connecting the S–A and A–V nodes. The specific histologic identification of these tracts and proving their physiologic role as conducting pathways constitute a major problem. The interatrial bundle, described by Bachmann,[2] was put on a sound basis since it has recently been conclusively demonstrated by electrophysiologic studies.[133]

After the conduction system of the heart had been described anatomically, investigations were instituted to establish the function of each component. The clinical and electrocardiographic manifestations of a malfunctioning pacemaker and conduction system were soon delineated. The following evidence indicated that the S–A node is the pacemaker of the heart: (1) embryologically, it is derived from the sinus venosus, which is the site of the pacemaker in cold-blooded vertebrates; (2) warming or cooling the node increases or decreases the rate of the heart; (3) injury to the node may alter the heart rate; (4) the classic experiments of Lewis[80] showed that, with each beat, the S–A node was the first portion of the heart to show negativity. Early investigators employed many methods of damaging the S–A node, including cauterization,[34,44] excision,[11,12,91] and clamping,[78] all of which produced marked slowing or disappearance of the normal sinus impulse.

The function of the A–V conduction system was established in the following manner. In 1905, Hering[34] damaged the bundle of His in four dogs. In three of them, the damage was sufficient to produce permanent complete A–V heart block. He also demonstrated that complete A–V heart block is not produced by lesions that interrupt the continuity of the A–V groove at locations other than the site of the specialized tissues. In 1907[21] and in 1909,[22] Erlanger and Blackman produced permanent complete A–V heart block in dogs by crushing the bundle of His under aseptic conditions. The dogs lived with complete A–V heart block for over 300 days. This experiment demonstrated not only the function of the bundle, but also the irreversibility of injury.

Eppinger and Rothberger[20] reported the effects of experimental interruption of both bundle branches: complete A–V dissociation resulted. They were also the first to demonstrate the electrocardiographic manifestations of interrupting one bundle branch at a time.

One of the earliest correlations between clinical heart block and the cardiac lesion at autopsy was made by Hay[33] in 1905. Other instances include that of a child reported by Armstrong and Mönckeberg[1] (1911), in whom complete block resulted from an endothelioma involving the A–V node, and Starling's patient[117] (1921) who developed complete A–V heart block unrelieved by atropine, and in whom a postmortem examination revealed a gross lesion of the conducting system.

Although the structure of the heart had been correlated with its functions, old concepts must now be reappraised in the light of investigations employing new techniques: recordings from single cells by intracellular microelectrodes and suction electrodes, the cardiac electrogram, and electron microscopy. This is discussed later in this chapter. The extensive electrophysiologic studies that have recently supported and refined the traditional concepts concerning the cardiac impulse are discussed in Chapter 2.

NORMAL ANATOMY

S–A Node

Embryology. The S–A node, the A–V junction, and the conduction system develop

by structural alterations of certain genetically predetermined cardiac muscle cells. The S–A node itself is derived from muscle cells of the right horn of the sinus venosus, which is incorporated into the developing definitive atrium in its superior left portion, medial to the entrance of the superior vena cava (Fig. 1–1). Meda and Ferroni, recording action potentials of single cardiac cells of a 13-somite (42-hour) chick embryo, were able to demonstrate the pacemaker in the sinoatrial area of the heart tube.[87] Van Mierop and Gessner identified the sinoatrial node in the 4.5-mm. mouse embryo (com-

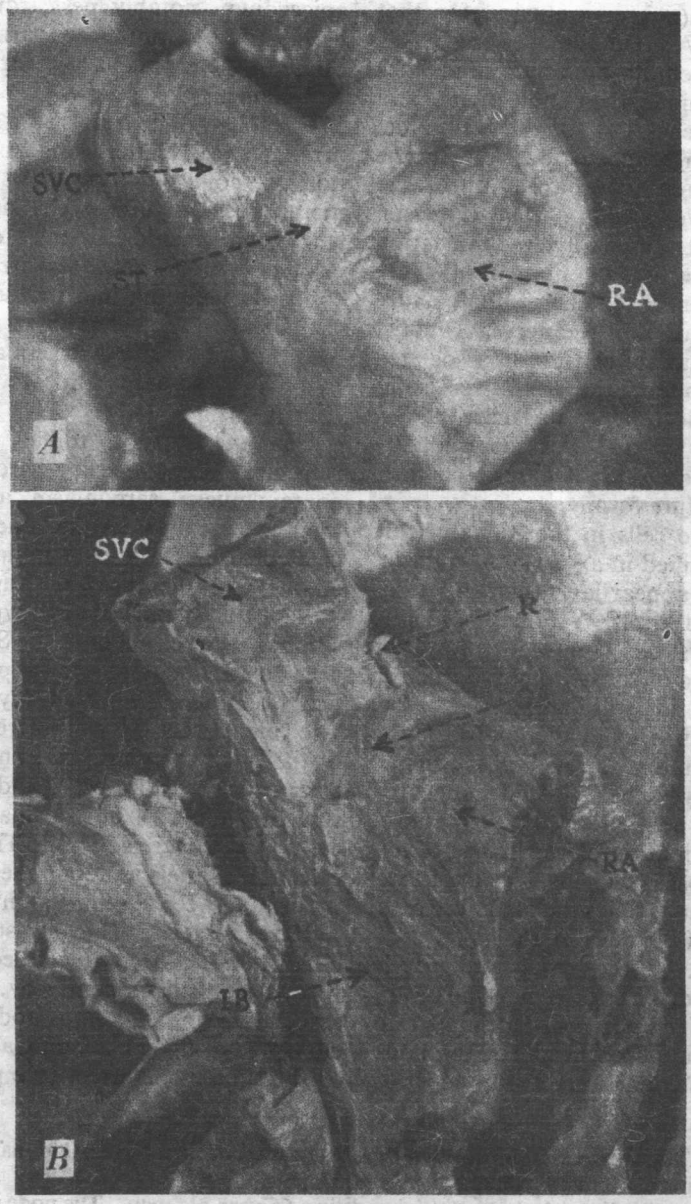

Figure 1–1. (*A*) Region of the sinoatrial node in a newborn child. *SVC*, superior vena cava; *ST*, sulcus terminalis; *RA*, right auricle. (*B*) Region of sinoatrial node with epicardium removed. *SVC*, superior vena cava; *SA*, sinoatrial node; *RA*, right atrium; *R*, recess of right atrium; *IB*, intercaval band. (Lev and Watne, courtesy of Arch. Path.)

parable to the 6.0-mm. human embryo) by light microscopy.[131] Walls[134] located the primordia of the S–A node in a 10-mm. human embryo. It consists of a group of closely packed cells with nuclei that have a stronger chromatin reaction than the atrial muscular cells surrounding it. At no stage of development (nor at maturity, for that matter) is the S–A node a grossly dissectible structure with definite boundaries, in contrast to the A–V node, the bundle of His, and the bundle branches. Also, the S–A node does not strikingly stand out under the microscope when compared with the surrounding myocardium. Nevertheless, Walls[134] felt that the characteristic location of this group of cells, the minor but definite histologic difference, together with the subsequent identification of the nerves, ganglia, and the artery that are constantly associated with the S–A node in the adult, were sufficient for identification at this early stage. The morphology of the S–A node gradually changes during gestation. Only at term does it assume its mature form.

Primitive nerve cells in the human heart can be first identified in a 16.5-mm. embryo. They, therefore, appear later than the primitive elements of the S–A node.[134] These nerve cells are first observed on the posterior epicardial surface of the atrium and in close relation to, but not within, the S–A node. Nerve fibers course from there toward the interatrial septum and the A–V junction.

Gross Anatomy. The S–A node is located in the superior portion of the right atrial wall at the termination of the sulcus terminalis.[71,72] In most specimens, it is not identifiable grossly, but at times the copious elastic tissue network of the node marks its location as a white area on the atrial wall. It is horseshoe-shaped, and its dimensions vary from 1.5 to 2.5 cm. in length and 0.4 to 0.7 cm. in width. The "head" of the node is located at the junction of the superior vena cava and the right atrium. It is subepicardial and courses to the left and inferiorly, ending subendocardially as the "tail," located at the junction of the auricular appendage and the atrium proper. Due to this unique position, the sinus node is affected by those processes which affect the epicardium, notably pericarditis,[48] and the endocardium, notably mural thrombi.[116] Some of the gross characteristics of the S–A node appear in Figure 1–1.

Histology. The cells of the sinus node are arranged in an interlacing network of supporting collagen to which the basement membranes of these cells are attached.[60] These interweaving bundles of fibers form clusters of nodal cells—an arrangement that contrasts with the more regular pattern of the atrial fibers. The S–A node contains much more elastic and collagenous tissue than the adjacent atrial myocardium[71] (Fig. 1–2).

Characteristically, ordinary cardiac muscle cells are surrounded by sarcolemma; they contain nuclei, sarcoplasm, and myofibrils; the fibers are cross striated and contain intercalated discs.[8] The S–A nodal cells possess all of these features to varying degrees. Two distinctly different cell types and a transitional cell type occur in the S–A node. The cells on the nodal margins appear to be identical to normal working myocardial cells. The central cells—P cells—are the main cells of the node; they are pale and thin in contrast to myocardial cells, and their internal structure differs from ordinary myocardial cells (see *Ultrastructure*). The transitional cells are, as their name implies, intermediate in form between P cells and myocardial cells.

Ultrastructure. The ultrastructure of the S–A node has been elucidated by many investigators, most recently by James and his associates.[58,60] The sinus node resembles an elongated cylinder extending along the course of the sinus node artery (see p. 31), with its

Figure 1–2. (*A*) Transverse section through the sinoatrial node in a 40-year-old man. *N*, Sinoatrial node; *A*, right atrium. Hematoxylin and eosin; × 57.

(*B*) Transverse section through the sinoatrial node in a 65-year-old man. The node is seen to the left of the viewer, with atrial musculature to the right. Hematoxylin and eosin; × 210.

(*C*) Section through sinoatrial node and atrial fibers to show myofibrils and striations. Note the small nodal fibers with relatively scant striations to the left of the viewer, as compared to the atrial fibers to the right. Phosphotungstic acid hematoxylin; × 871. (Lev and Watne, courtesy of Arch. Path.)

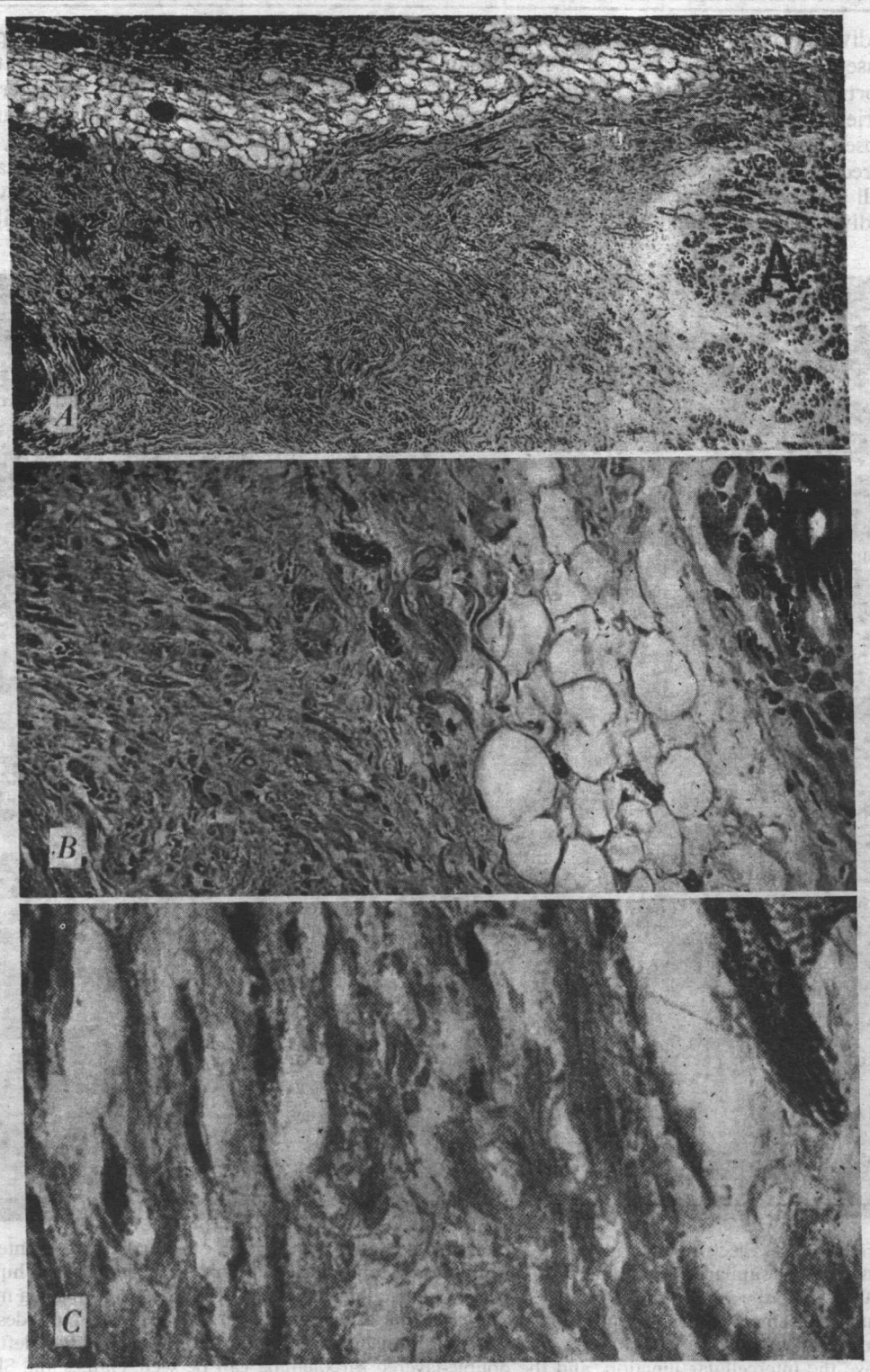

Figure 1–2. Legend on facing page.

individual cells attached by means of their basement membranes to a network of supporting collagen fibers.[60] Numerous capillaries, fibrocytes, and nerve endings may be observed in the intercellular spaces, but no direct contact between nerve endings and cell surfaces have yet been described.[60] The individual cells of the human S–A node may be divided into four groups: (1) P ("pacemaker") cells located predominantly at the center of the node (Fig. 1–3); (2) undifferentiated myocardial cells, located mostly at the border of the node; (3) transitional cells, with structural properties and often a location that is intermediate between the previous types (Fig. 1–4); and (4) Purkinje fibers,

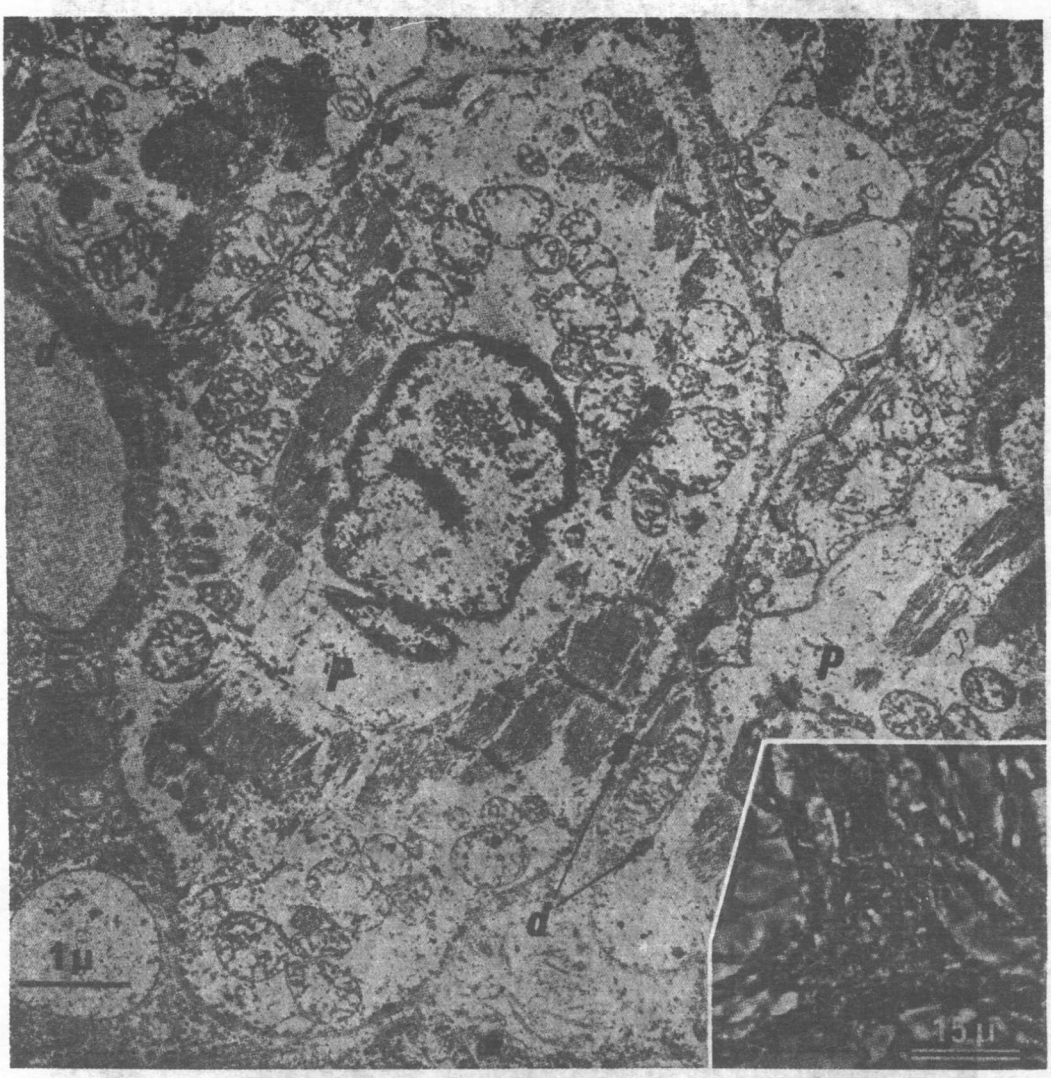

Figure 1–3. Electron micrograph of P cells from human sinus node. Note the simple internal structure. A similar cell examined by light microscopy and phase illumination is shown from human sinus node in the *inset* at the right lower corner. Intercellular junctions of P cells are by plasma membrane to plasma membrane apposition (*small open arrow* at the upper left) with a few scattered desmosomes, indicated by *d*. The *small short black arrow* in the upper left indicates an intercellular cleft just above the intercellular junction, and the double-layered sarcolemma can be seen. (James and Sherf, courtesy of Amer. J. Cardiol.)

found at the borders of the node, extending to the atrial muscle and to the specific conduction pathways.[58]

P cells differ strikingly from other cells of the myocardium.[58,60] They are small, relatively smooth and round in outline, and are gathered in clusters within a single basement membrane, which in turn makes contact with collagen fibers.[63] Their fine structure is characterized by a relative paucity of myo-

Figure 1–4. Electron micrograph of human sinus node showing particularly well one of the slender transitional cells (*Tr*), the ends of which are indicated with two open arrows. Note the orderly parallel array of myofibrils and the abundant number of filaments per fibril, in contrast to P cells. At least four P cells are labeled *P* in the upper half of the picture, and the tip of a fifth one lies just below the *Tr* cell. The nucleus near the middle at the top is in an unidentified cell, probably fibroblast, as is the nucleus lying parallel to and just above the *Tr* cell. The large vacant spaces probably represent fat cells, while *C* indicates collagen fibrils. (James and Sherf, courtesy of Amer. J. Cardiol.)

fibrils, which are oriented randomly, a decreased number of sarcomes (mitochondria) and cytoplasmic granules (glycogen), and an absence of intercalated discs combined with a relatively small number of *desmosomes* and *nexus* structures (see Fig. 1–3). One end of a transitional cell might resemble a P cell and the other end, a myocardial fiber, or a transitional cell might be homogenous, having an intermediate number of myofibrils, sarcosomes, intercalated discs, and nexus structures (Fig. 1–4). (Purkinje fibers are discussed on p. 20; the ultrastructure of undifferentiated myocardium is described in many communications.[8,15,58,60,63]

A number of studies have been performed and many theoretical considerations invoked to determine the functional significance of the cells of the S–A node. The P cells were originally believed to have a pacemaking function, as suggested by their appearance under the light microscope and their apparent relationship to nerve endings (they appear closer to nerve endings under the light microscope than they do under the electron microscope.)[47] Structurally similar cells assume the pacemaking function and manifest the electrophysiologic characteristics of automaticity in tissue cultures.[16,30,31,94] The pacemaker cells of the *in vivo* sinus node of the rabbit have a similar ultrastructure.[125] Similar cells are observed in smaller numbers in the A–V junction.[59]

The structural features of cardiac cells can be correlated with the speed of conduction through them. Small cells conduct less rapidly than larger cells,[15] and cells with little endoplasmic reticulum manifest slower intracellular conduction.[27,88] Intercalated discs may facilitate conduction,[58,135] and the consensus is that nexus structures promote conduction between cells.[15] P cells are characteristically small, have little endoplasmic reticulum, and present few connections to adjacent cells. Conduction through them might then be expected to be slow, as in fact it is.[36] This may be a basis for the slow conduction through the S–A node.[39]

Atria

The fibers of the S–A node are in continuity with various specialized cell types. These consist of (1) the transitional cells, discussed previously; and (2) specific pathways that extend from the S–A node to the A–V junction, the left atrium, and probably portions of the atrial musculature located at a distance from the sinus node. The recent evidence for the existence of these specialized pathways has required revision of the long-held concept that the impulse proceeded from the S–A node by simple radiation over undifferentiated atrial myocardium.

When Keith and Flack[64] first described the S–A node in 1907, they suggested that direct internodal muscular connections might conduct impulses. Subsequently, Wenckebach[136] described a pathway of Purkinje-like fibers extending down the posterior wall of the right atrium adjacent to the atrial septum and terminating at the A–V node. Two years later, Thorel[122] demonstrated a direct pathway between the two nodes following the course of the crista terminalis.

Eyster and Meek[23,24,88] performed a series of experiments, the results of which they interpreted as supporting the concept of internodal conducting pathways: appropriately placed incisions in the right atrial wall caused conduction abnormalities, suggesting that the normal pathways had been blocked. However, Lewis and his associates,[81,82] who had participated in establishing the role of the sinus node as a pacemaker, held that conduction was by radial spread of the impulse through the atrial muscle. This theory of conduction came to be generally accepted. Only the interatrial conduction bundle, described by Bachmann[2] in 1916, was considered an exception; however, its role was not clearly defined.

Anatomists have periodically reported finding internodal pathways. Robb, Kaylor and Turman[104] observed that the S–A and A–V nodes in the 15- to 32-week-old fetus are connected by four distinct pathways consisting of specialized and nonspecialized muscle cells. Robb and Petri[103] also presented further anatomic evidence of internodal tracts in human and monkey atria. On the other hand, Truex[126] and Lev[73] denied the existence of atrial tracts composed of special fibers.

Meanwhile, physiologic evidence for functioning specialized atrial tissue was also accumulating. Takayasu and co-workers[120]