# Chance and Sudden Death

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**An aura of mystery has always surrounded the subject of sudden unexpected death. Part of the explanation is an absence of a single or usual explanation, although electrical instability of the heart does serve as a unifying concept for the final common pathway. In this review, emphasis is placed on the random aggregation of a wide variety of contributing factors in the pathogenesis of sudden death. Such factors include coronary disease, platelet aggregation, neural control of the heart, apoplexy of the heart, normal and abnormal variations in the structure of the atrioventricular junction, lessons from certain rare cardiac tumors and the nature of ventricular fibrillation. Useful thinking about these and related causes should employ both a horizontal (concurrence of events) and vertical (sequence of events) matrix, in all of which chance plays a major role. One impediment to understanding sudden death associated with coronary disease is the prevalent assumption that one is due to the other without proper examination of the other factors involved, some of which may be more susceptible to intervention or modification. The multifactorial nature of the pathogenesis of sudden death and the recognition that chance is a major determinant of which factors convene and when they will aggregate in the victim are essential elements to consider if more effective means of treatment and prevention are to be obtained.**

Death hath so many doors by which to let life out.
Beaumont and Fletcher, "The Custom of the Country."

No one much wants to think about dying, but the idea that sudden death might largely be a matter of chance is particularly unappealing. Beyond the possibility that such a thought could generate undue anxiety or apprehension, it seems to be a singularly unscientific concept. In science we want things to be more orderly and predictable. But if it is true that many or most instances of sudden death cannot be predicted even with the most sophisticated diagnostic procedures available, then we will need to accept this truth and perhaps rearrange our thoughts on the subject. To prevent a possible misinterpretation of this discussion, let me state that there is no intent to espouse therapeutic nihilism or hopelessness. On the contrary, I believe that only by recognizing the mulitfaceted nature of sudden death and the major element of chance inherent in the presence or significance of a large number of contributing factors can we hope to develop and appropriate strategy to deal with as many of these factors as possible. As a corollary, there are some factors for which there is now no way to intervene, and in these circumstances, we will be challenged to increase our understanding so that treatment or prevention becomes possible.

In most cases of sudden and unexpected death, there is little doubt that the terminal event is some form of lethal electrical instability of the heart. Considered from a numerical standpoint, the great majority of such sudden deaths occur in persons with extensive coronary disease. But considered from other standpoints, there is equally strong interest in the unexpected death of babies (crib death or cot death), young athletes or even certain animals such as dogs or racehorses. Although these may seem unrelated subjects, they are on the contrary a rich source of lessons applicable to a surprising extent to all examples of sudden unexpected death. It is one purpose of this review to explain why this is so.

Unlike many diseases that end in death, a fatal arrhythmia is most often remarkably brief. This makes the logical challenge of prevention especially intriguing. Much effort has been and is currently being directed to the identification of

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J AM COLL CARDIOL
1983;1:164–83



clues on which to base prediction about sudden death, for the purpose of devising preventive measures. Particular attention has been focused on the careful definition of premature beats or other forms of manifest electrical instability of the heart, but to be valid predictors, these phenomena should have a consistent or fixed pattern in future periods of instability. Such a concept is at the very least debatable and quite likely a paradox in logic, because many forms of instability are inherently unpredictable.

Another purpose of this review is to illustrate how large a role chance plays in the pathogenesis of sudden death, or in the risk of its happening. Recognition of this principle—that sudden death is largely a matter of the chance aggregation of circumstances—should redirect us from so much emphasis on seeking a treatment or prevention of the terminal events themselves, which may never be truly possible, to a more careful examination of the variety of important prior contributing causes that may be more amenable to interdiction or reversal. Many of these precursors have received too little attention.

## Physiologic and Anatomic Substrates of Sudden Death

For many years my personal research interest has been the structure and function of the conduction system of the heart, particularly but not exclusively as these subjects may relate to the pathogenesis of sudden unexpected death. One lesson from this accumulated experience is that, although ventricular fibrillation or standstill may be the ultimate physiologic fault, there is no single anatomic substrate. This is not to say that there are no anatomic abnormalities. Quite the opposite is true. In virtually every heart from examples of sudden unexpected death suitably studied, there is at least one and more often there are multiple anatomic abnormalities. These may be within the large or small coronary arteries (particularly those supplying crucial elements of the impulse-forming and conduction system), in the myocardium (especially ventricular hypertrophy) or in the cardiac nerves and ganglia. Each of these anatomic abnormalities is a potential cause of electrical instability.

Some of these anatomic changes can also be seen in the hearts of those who die in a way not usually classified as sudden or unexpected. However, these latter subjects can seldom if ever be accepted as true "controls" for several reasons. First, they too are dead, and the exact terminal event is rarely known accurately (for example, even patients with advanced cancer or cirrhosis or automobile accident victims may have actually died of ventricular fibrillation). Second, any single anatomic abnormality must be interpreted in the context of other functional or anatomic changes that may augment or diminish its individual significance. Finally, as yet we know far too little of the actual functional significance that may be attributed to congenital variations or acquired diseases involving the cardiac conduction system to reject any of them as potential factors in the risk of sudden death.

What we can deduce is that sudden unexpected death may be the ultimate game of chance in life. The combination of certain anatomic abnormalities or variations may be the exact "suitable substrate" to which Engle (1) refers when discussing the subject. An unknown but probably very large number and variety of transient intercurrent influences, many perhaps truly innocuous alone, can add to the likelihood of lethal electrical instability of the heart. This is exactly what Pruitt (2) meant in describing sudden death as an expression of functional disease.

How chance helps determine when and in what way one may die suddenly will be examined from seven perspectives, in each of which a consideration of structure and function will be interwoven. The first three subjects are coronary disease, blood platelets and neural control of the heart. The fourth topic is apoplexy of the heart, wherein the reciprocal influences of heart and brain are reviewed. The fifth subject deals with structure and function of the atrioventricular (AV) junction and how electrical stability of the heart may be influenced there. The sixth topic is the lessons to be learned from certain tumors of the heart associated with sudden death. Fittingly, the last subject is ventricular fibrillation, which is often the terminal event but of itself may teach us much less about preventing sudden death than can many earlier changes, both anatomic and physiologic.

## Coronary Disease and Sudden Death

Some examples of this relation require little discussion here, because cardiac rupture, progressive or sudden congestive failure, and cardiogenic shock with or without acute myocardial infarction are all major separate subjects. However, although electrical instability may be the sole fatal event in a patient with coronary disease, no other catastrophe being present, it may also be the essential terminal event for any of these other catastrophes, or it may be a key factor among events serving as a prelude in the actual pathogenesis of infarction or failure or shock.

**Variables that determine functional significance of coronary disease.** When seeking to understand how coronary disease may relate to sudden death it is not sufficient to say that there was severe coronary narrowing or that there was diffuse coronary disease. Nor is it especially useful to consider the size or location of myocardial ischemia or infarction without also considering the specific cardiac structures that were included. In evaluating the functional significance of human coronary disease at least six variables require careful consideration. These are 1) the size and surface integrity of any atheroma or similar fixed narrowing lesion, 2) a best estimate of myocardial oxygen demand at

the time of trouble or death, 3) a best estimate of effective coronary perfusion pressure, 4) the extent and function of available collateral circulation, 5) the presence or absence of platelet aggregations or emboli, and 6) the exact structure that is supplied downstream from any detected narrowing lesion. The fact that it is difficult and perhaps impossible (with present methods) to assess or quantify certain of these variables does not diminish their importance.

**Size and surface integrity of coronary atheroma.** An atheroma that completely occludes or greatly narrows a major coronary artery has a rather straightforward significance. However, lesser lesions are often dismissed too readily, especially when seen on a coronary arteriogram. The surface integrity of an atheroma plays an important role in its functional significance. When carefully examined, as in the classic study by Osborne (3), abnormalities of the surface of an atheroma are surprisingly often associated with downstream embolization either of debris from the atheroma or of platelets or other clot fragments probably originating from the rough surface of such lesions. Furthermore, there is growing appreciation of the role of spasm as a transient cause of coronary narrowing, and recognition that spasm is more prone to occur at sites of some anatomic abnormality in a coronary artery.

**Myocardial oxygen demand, perfusion pressure and collateral vessels.** While a patient is alive it is difficult to estimate the true level of myocardial oxygen demand, in part because of its continuing variability. At the same time there can be no doubt that an atheroma narrowing a coronary artery by 80% has a different significance if the myocardium it perfuses is or is not working very hard. Similarly, such a lesion would be more serious if central aortic pressure were low and right atrial pressure were high, thus reducing effective coronary perfusion pressure, than if both of these pressures were normal. Many different factors contribute to the determination of either delivery or distribution of coronary collateral circulation (4), but any given coronary narrowing has a significance that depends importantly on whether collateral circulation is or is not available beyond the narrowing. Platelet aggregation on any coronary lesion alters the significance of a lesion from one that can be attributed solely to the original lesion's luminal encroachment, but

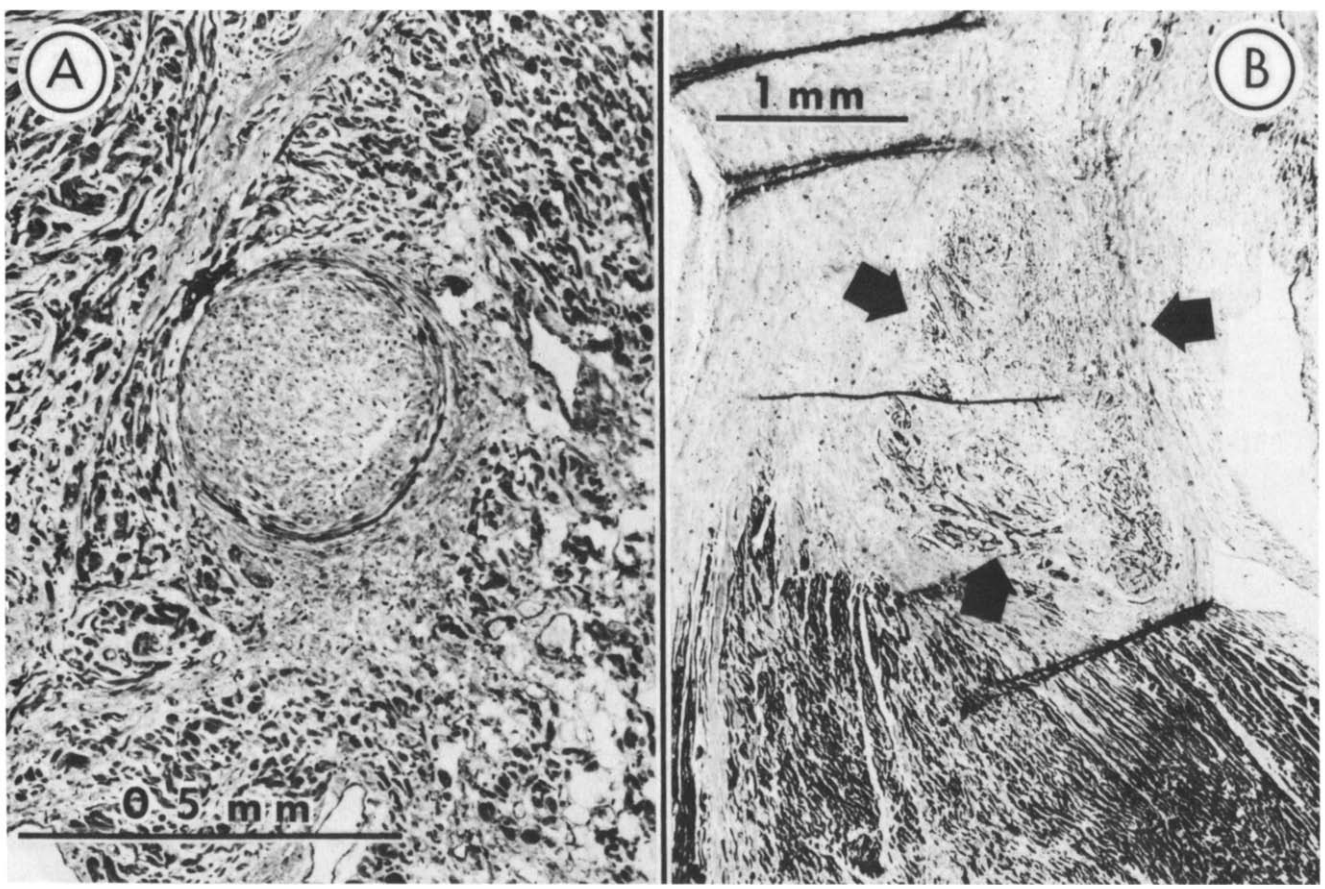


**Figure 1.** This photomicrograph illustrates occlusion of the AV node artery by focal fibromuscular dysplasia (**A**). Downstream there was complete disruption of the His bundle (**black arrows** in **B**) by chronic fibrosis. This young man died with complete heart block. Goldner trichrome stain was used in all photomicrographs unless otherwise indicated. Magnification is depicted with reference bars. (Modified from James TN, et al. [6,12,13,29,32, 44], by permission of the American Heart Association, Inc.)

J AM COLL CARDIOL
1983;1:164–83



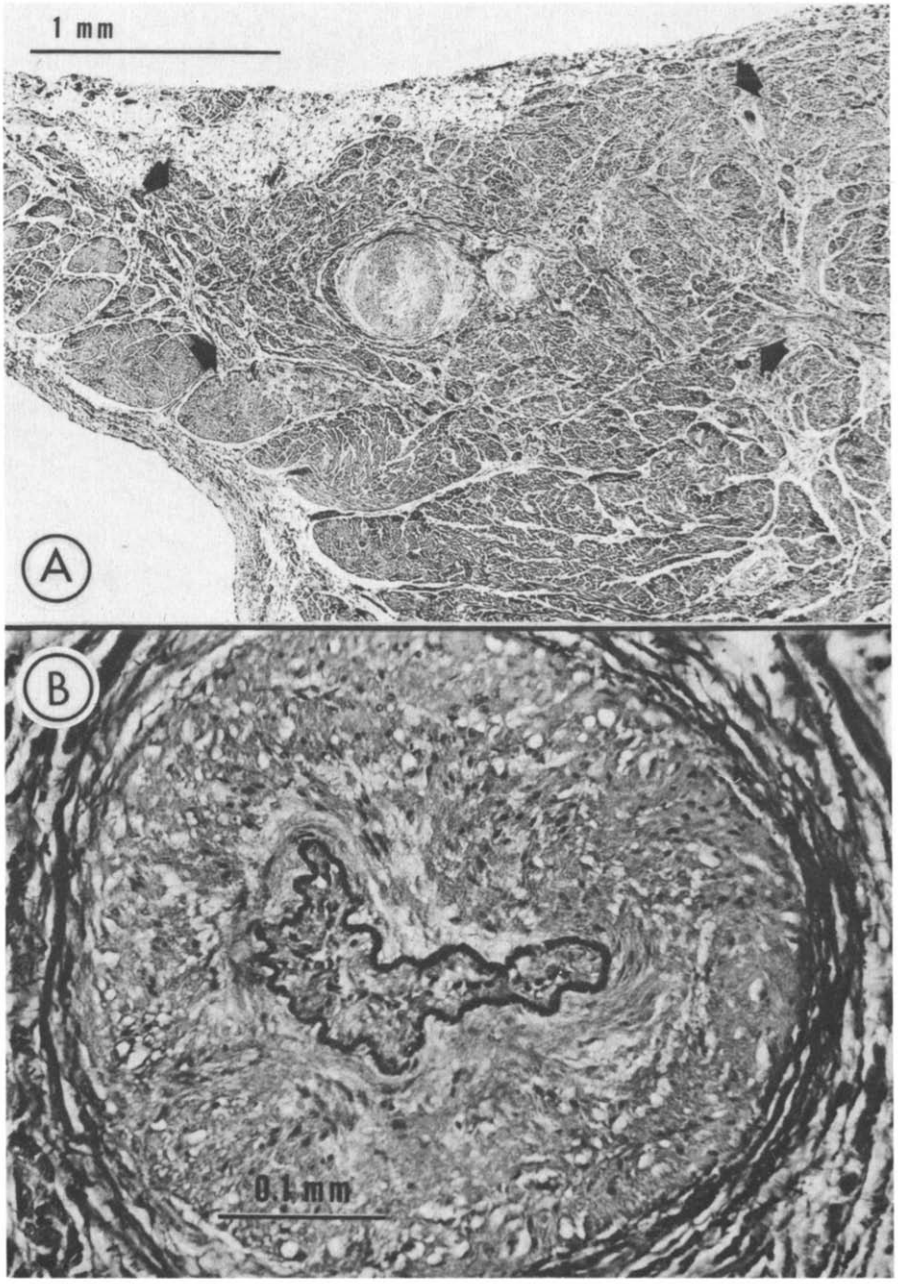


**Figure 2.** Sinus node of a young athlete who died suddenly and unexpectedly is shown between **black arrows** in **A**. Focal fibromuscular dysplasia obliterates the lumen of the sinus node artery seen at higher magnification in **B**. Verhoeff-van Gieson elastic stain was used in **B**. (Modified from James TN, et al. [30], with permission.)

other aspects of platelet aggregation are equally important and will be discussed separately.

**Site and number of obstructions and structures supplied downstream.** Finally, in virtually all grading or classifying schemes that deal with the significance of coronary disease, too little attention is offered to the structure that the narrowed artery was supplying (Fig. 1 to 3). For example, saying that a patient had one vessel, two vessel or three vessel disease (what may be called the ultimate strike-out of baseball cardiology) means little without also considering exactly where the obstruction was located, how many other obstructions also existed in the same and other vessels and which structures were supplied downstream from the obstruction. Although multiple severe narrowings of the left anterior descending artery have a different significance from that of only one narrowing in the midportion of the same artery, both are examples of "single vessel disease." Similarly, a proximal severe single narrowing of a left circumflex artery that crossed the crux of the heart and supplied not only most of the lateral and posterior left ventricle but also the AV node (also single vessel disease) differs significantly from an identical lesion located in the proximal left circumflex artery if the vessel is very short. A proximal right coronary occlusion would have a completely different

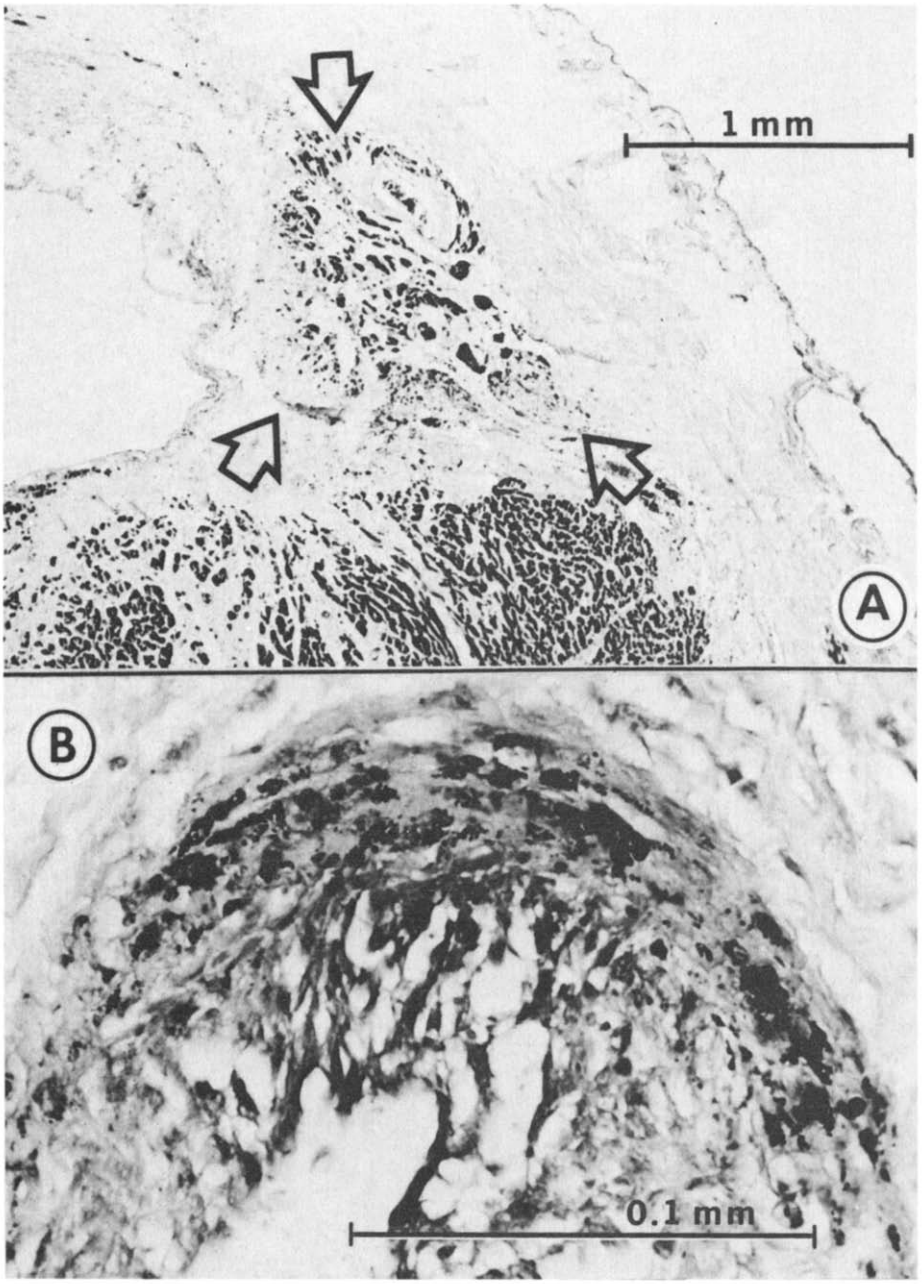


**Figure 3.** Fibrotic degeneration of the His bundle (**arrows** in **A**) is shown from the heart of a patient dying with Whipple's disease. Medial degeneration and intimal proliferation are shown in a left ventricular artery of this same patient in **B**. Nutrient arteries to the His bundle were similarly narrowed. Bacilliform bodies within the tunica media (**B**) appear black. Periodic acid-Schiff stain.

electrophysiologic significance depending not only on whether it crossed the crux of the heart to supply much of the posterior left ventricle, as it does in 90% of human hearts (5), but also on whether the sinus node artery or the AV node artery was a branch arising distal to the point of occlusion.

## Platelets and Sudden Death

Platelets, the smallest of our blood cells, were thought as recently as 50 years ago to be nothing more than artifacts present in blood smears. Today they are recognized as crucial elements in the process of coagulation, as well as the cellular storehouse within the circulation for a wide variety of vaso-active substances. For example, thromboxane A, which is released from platelets, is an especially powerful coronary vasoconstrictor and may be the basis for some examples of human coronary spasm. Virtually all of the circulating serotonin (5-hydroxytryptamine) is carried by the platelets and released by them when platelets aggregate. Serotonin released from intracoronary aggregation of platelets may be responsible for a cardiogenic hypertensive chemoreflex (6), expressed clinically as the severe but transient hypertension sometimes appearing during angina pectoris (7,8) or very early in acute myocardial infarction (9,10).

J AM COLL CARDIOL
1983:1:164–83



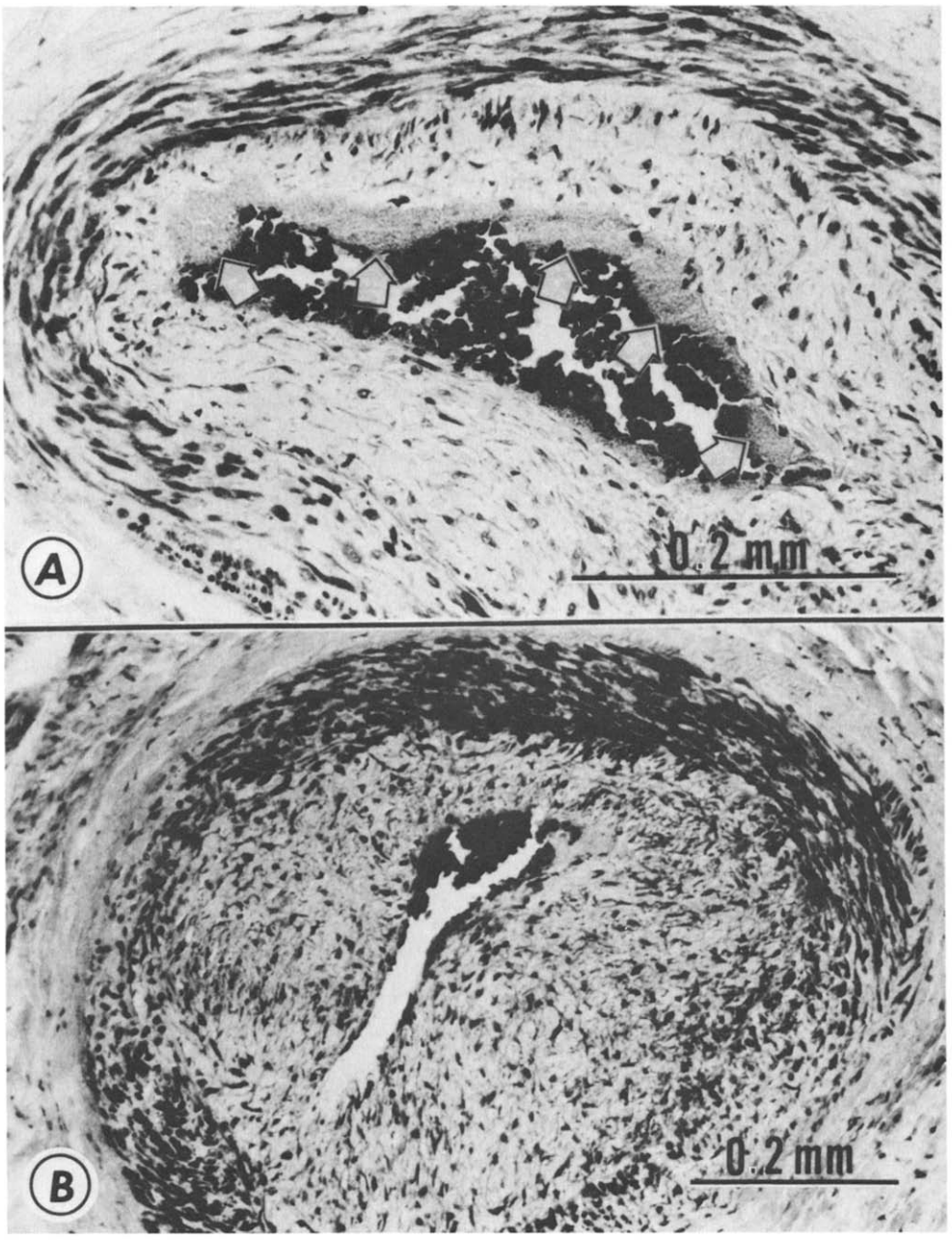


**Figure 4.** Marked intimal proliferation narrows the lumen in two different sections of the AV node artery of a child dying with congenital homocystinuria. A layer of platelets (**arrows** in **A**) is silted against the endothelium. (Modified from James TN, et al. [6,12,13,29,32,44], by permission of the American Heart Association, Inc.)

**Role in coronary obstruction and arrhythmias.** In addition to the mischief for which platelets can be responsible by the release of vasoactive or receptor-stimulating substances, and their familiar role in thrombosis, they are increasingly becoming suspect as a cause of transient coronary obstruction, particularly within the smaller arterial branches (Fig. 4 and 5). The problem with this latter concept is that loosely aggregated platelets tend to disaggregate and disappear and are no longer demonstrable morphologically, even if they have been an effective obstruction of the coronary circulation for a long enough time to cause permanent myocardial ischemic damage (11). Such a potentially damaging or even lethal form of evanescent obstruction poses an unpalatable dilemma for the pathologist, making postmortem clinicopathologic correlations difficult and sometimes impossible; transient platelet obstructions cannot be

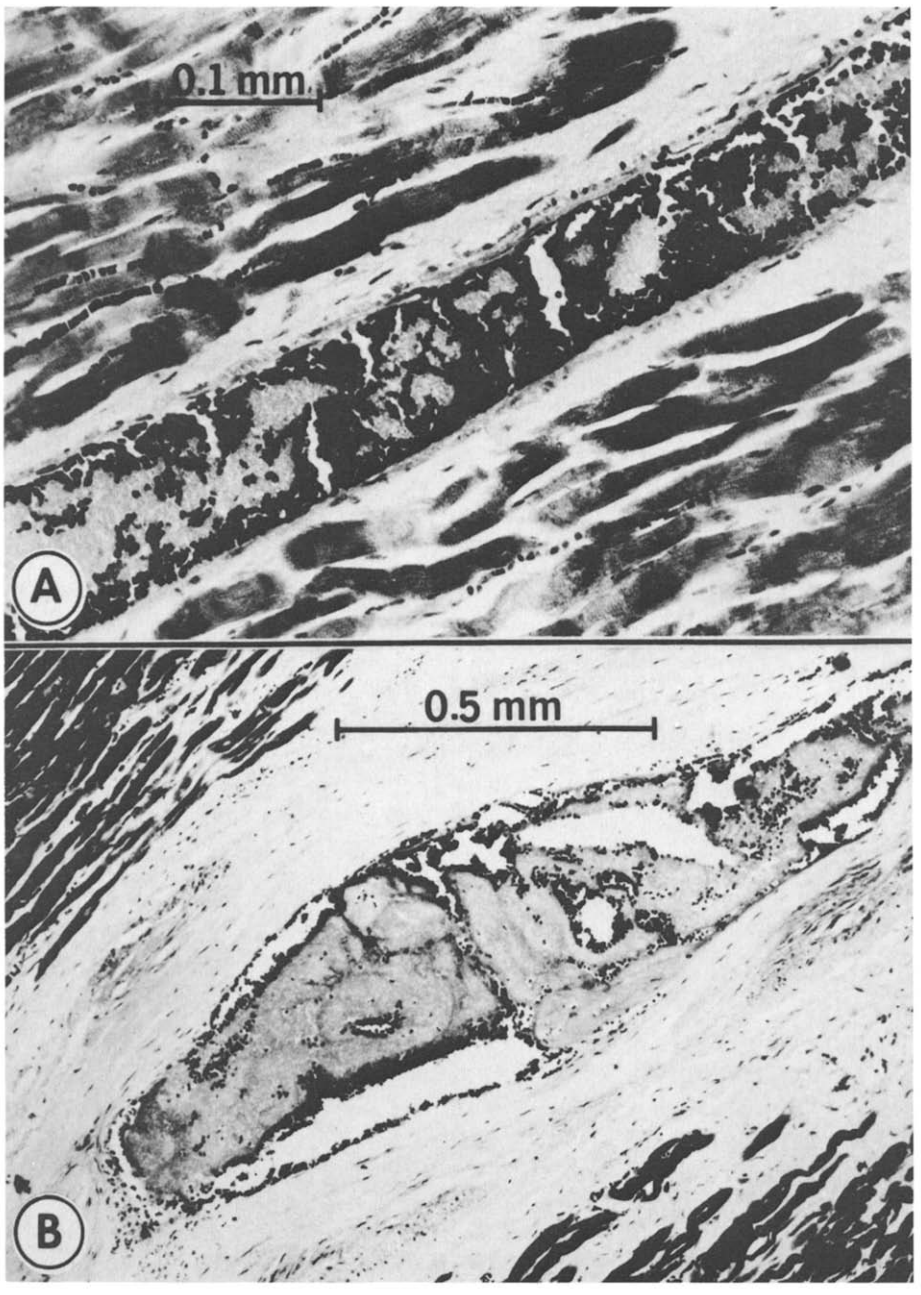


**Figure 5.** Intraarterial platelet aggregations are shown from the left ventricle of a patient dying with pheochromocytoma. Recent aggregates are shown in **A**; older ones are shown in **B** where a black fibrin coat is seen. Phosphotungstic acid-hematoxylin stain in **B**. (Modified from James TN, et al. [6,12,13,29,32,44], by permission of the American Heart Association, Inc.)

ruled in or out. Nevertheless, the bulk of available evidence supports the likelihood that transient platelet aggregations within the coronary circulation may be responsible for some arrhythmias or conduction disturbances encountered in the clinical course of patients with chronic coronary disease. Intracoronary platelets have been demonstrated and may be responsible for lethal electrical instability causing sudden death in patients with pheochromocytoma (12), congenital homocystinuria (13), thrombotic thrombocytopenic purpura (14) or disseminated intravascular coagulation (15).

## Neural Control of the Heart and Sudden Death

Nearly every familiar function of the human heart is powerfully influenced by the autonomic nerves. Two forms of neural influence are the continuous or "tonic" activity of the autonomic nervous system and the powerful surges exemplified by many reflexes that profoundly alter cardiac performance. In a discussion of sudden death, it is particularly relevant that the autonomic nervous system exerts

such a remarkable influence on the processes of impulse formation, cardiac conduction and myocardial repolarization. Although it has long been appreciated how abnormal rhythms or heart block can result in lethal electrical instability, only in the past few decades has it become generally recognized that abnormal forms of *repolarization* can be the fundamental fault, as illustrated by the growing experience with the long QT syndrome (16).

Given that the nerves have such an important effect on both normal and abnormal cardiac performance, it is surprising that they have received so little attention in postmortem studies. With the notable exception of Rossi (17) and very few others, workers conducting postmortem correlative studies even in cases of sudden unexpected death have taken little note of the condition of the intracardiac nerves and ganglia. It is, of course, recognized that intracranial and other extracardiac neural centers or trunks can exert an abnormal neural influence on the heart, but in the present discussion my comments will be confined to those changes that may be collectively designated as forms of *cardioneuropathy*.

Toward the end of the 19th century, fierce debates raged between those who thought that all electrical activity of the heart was neurogenic and those who claimed that it was myogenic. Although the evidence today leaves no reasonable doubt that impulse formation and conduction occur exclusively in special myocytes, which now are the focus for many forms of research, it is regrettable that anatomists seem to have lost interest in the nerves of the heart. Compared with the universal and careful attention given, for example, to the large coronary arteries, analogous descriptions of cardiac nerves or ganglia are virtually nonexistent. This is true even though, for the sake of electrical stability of the heart, its nerves must be as important as its coronary arteries. Transplanted hearts can, of course, function in a stable fashion, but this may be partly because they are equally unsusceptible to either the unstabilizing or the stabilizing influence of the nerves and ganglia, which are indisputably very active in virtually *all* other human hearts. In other words, in everyone except those with a transplanted heart, the autonomic nerves continually influence cardiac performance, and we need to know more about that.

**Cardioneuropathy.** It requires no more than ordinary curiosity during any careful postmortem study of the heart to find distinct forms of cardioneuropathy in patients dying with ischemic heart disease (18), lupus erythematosus (19), polyarteritis nodosa (20), Whipple's disease (21), sarcoidosis (22), scleroderma (23), Friedreich's ataxia with cardiomyopathy (24) or diphtheria (25), to mention only a few examples. In truth almost any diffuse myocardial disease randomly and sometimes selectively involves the nerves. Some illustrations of neural selectivity can be found in reports of sudden unexpected death observed in the long QT syndrome (16), familial forms of syncopal arrhythmias (26) and otherwise unexplained automobile accidents (27) in which the cardioneuropathy is either the predominant or exclusive abnormality found (Fig. 6). Although the etiology of potentially lethal cardioneuropathy has not been established, some form of viral infection must be ranked high among the possibilities (28). There is now a growing recognition of the chronic nature of certain viral infections. Herpes varicella-zoster virus, for example, is probably harbored for life and only sporadically activated as either chicken pox or shingles. This knowledge compels us to reconsider whether sudden unexpected death seen in certain families has any true genetic or heritable basis, as has been supposed in the long QT syndrome, or whether these tragedies are expressions of some insidious and chronic infection harbored and shared within the family.

*Ganglionitis or neuropathy within the heart could be responsible for distortion of impulse formation, impairment of conduction or altered repolarization.* Neural disease could similarly be responsible for initiating cardiogenic reflexes, disorganizing the sequence or the focal power of myocardial contraction or, perhaps, even reducing the caliber of certain coronary arteries. Any of these consequences could produce an undesirable distortion of the electrical activity of an otherwise normal heart (except for its nerves). If one adds any of a variety of structural variations to such postulated neurogenic destabilization of a normal heart, the significance of the neural control is compounded. For example, minor narrowing of certain nutrient arteries (29–31), persistent fetal dispersion of the otherwise normal AV node or His bundle (32) or the presence of some degree of fever, toxicity or mild acidosis could become disastrous, given a concomitant distortion of neural control of the heart. Transient platelet aggregations could be either a compounding factor by causing focal ischemia, or a directly responsible initiating factor by releasing serotonin and activating the neuroreceptor (Fig. 7) responsible for the cardiogenic hypertensive chemoreflex (6).

**Subtraction phenomenon.** Up to this point we have reviewed the neural influence of cardiac electrical activity that is expected when reflexes are activated or when efferent neural traffic is disorganized. In addition, we need to consider what may be called the *subtraction phenomenon,* which is seen when an expected normal response by the heart fails to occur because of neural disease. A specific example is the random coexistence of an effectively "denervated" sinus node and a relatively normal AV node. It is to be anticipated that under such circumstances, any vagal reflex would fail to slow the sinus node but would have its usual negative dromotropic effect in or near the vicinity of the AV node. Experimentally it is simple to mimic these circumstances (33). Although the reflex heart block demonstrated experimentally is relatively brief (Fig. 8), it would be capable of

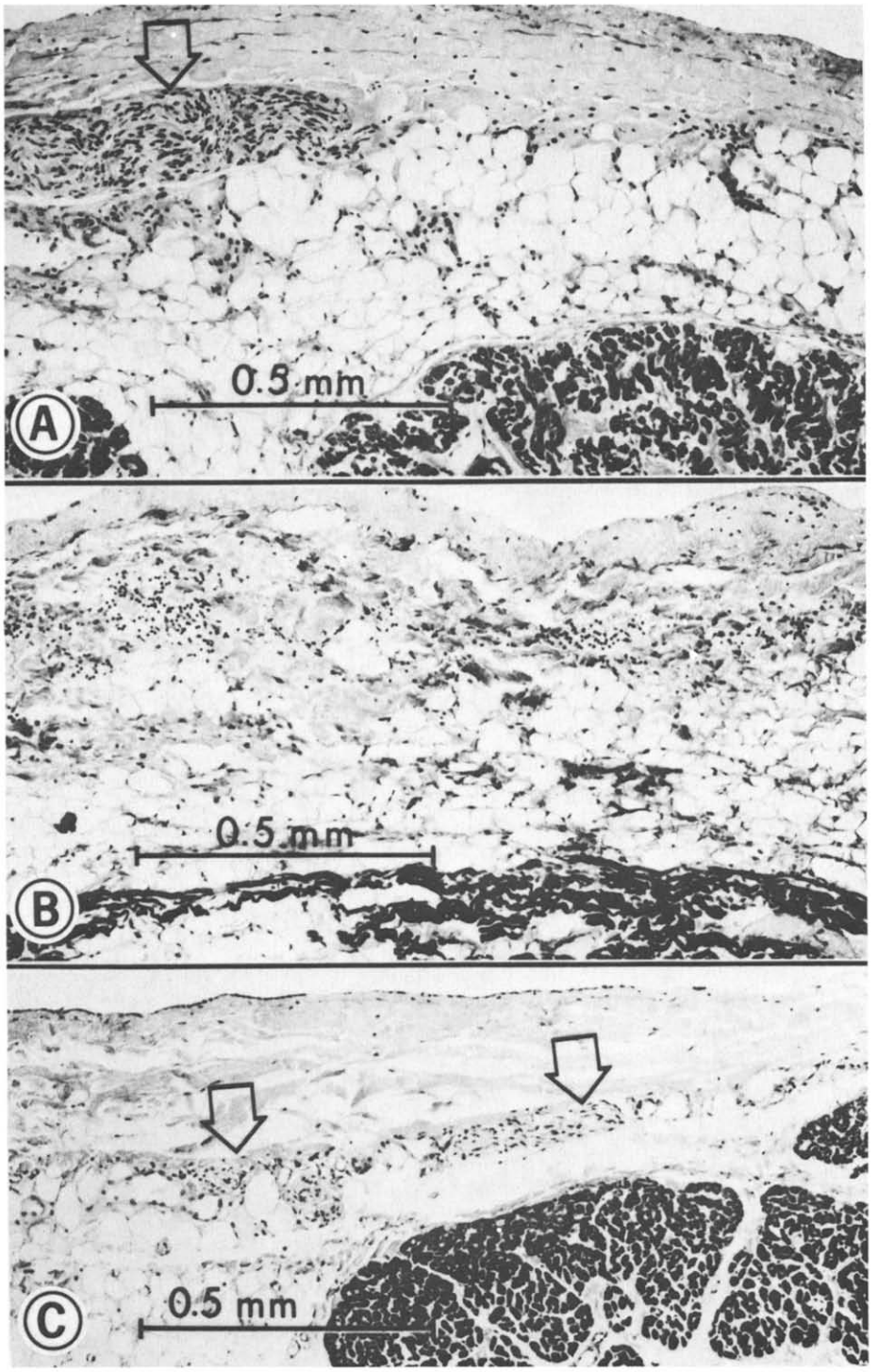


**Figure 6.** Focal neuritis and vesicular neural degeneration from the vicinity of the sinus node of a patient dying with multiple arrhythmias in association with the long QT syndrome. A large nerve (**arrow**) is shown with adjacent inflammation in **A**, disrupted nerves and inflammation are seen in **B** and vesicular degeneration of a long nerve (**two arrows**) is shown in **C**. All of these examples are located just beneath the epicardium, but there is no pericarditis. (Reprinted from James TN [28], with permission.)

causing catastrophe if there was any focal irritability in a hypertrophied left ventricle. For these and many of the preceding hypothetical situations and combinations of circumstances, a key consideration is that such coincidences are greatly due to chance and their predictability is limited.

## Apoplexy of the Heart and Sudden Death

Undoubtedly the form of apoplexy most familiar to physicians is that afflicting the brain, although there has been some clinical attention to apoplexy of the pituitary gland and to adrenal apoplexy. Every form of vascular disturbance

J AM COLL CARDIOL
1983;1:164–83



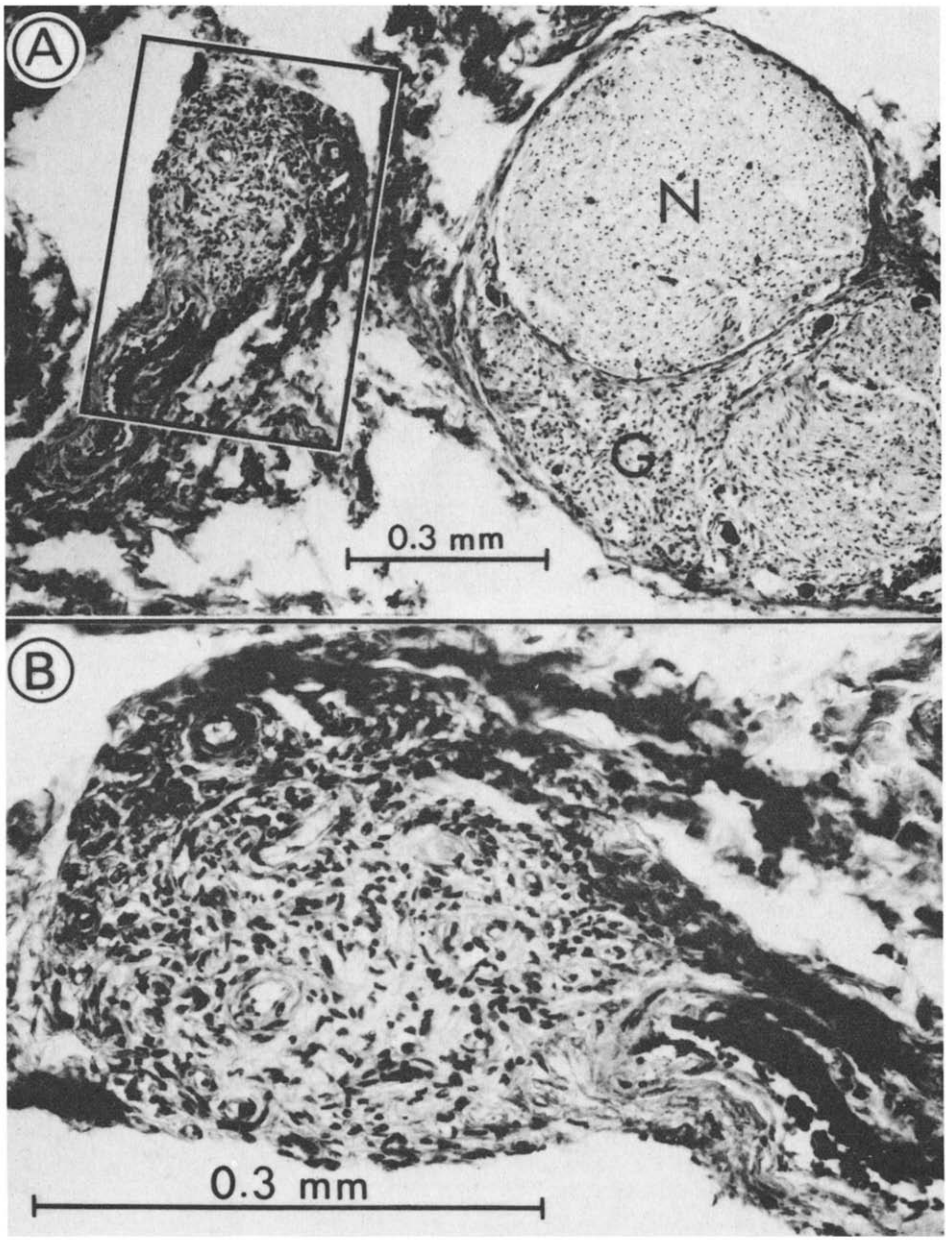


**Figure 7.** The chemoreceptor responsible for the cardiogenic hypertensive reflex is boxed in **A** and shown at higher magnification in **B**. N is a large nerve and G is a ganglion in this human heart. The nutrient artery of the chemoreceptor originates from the main left coronary artery. (Modified from James TN, et al. [6,12,13,29,32,44], by permission of the American Heart Association, Inc.)

that can end in cerebral apoplexy can also exist in the heart, some examples being coronary artery thrombosis, embolism or rupture (18). Furthermore, there are many close analogies between the combined neural and vascular malfunction seen in the brain and that seen in the heart. Both organs contain intricate control systems that are readily deranged by vascular accidents. Medical problems originating with a cerebrovascular accident often culminate in altered myocardial electrical activity; the giant T waves of a stroke victim (34) are one such example. Conversely, an unknown but probably large number of cerebrovascular events begin with an original disturbance of cardiac rhythm or conduction, as epitomized in Stokes-Adams attacks.

*Chance concurrence of events in the brain or the heart leading to sudden death can clearly originate in either organ and quickly influence the function of the other.* Although the original event in either the brain or the heart can be vascular (apoplexy), the consequences in both organs include neural malfunction. If the first event is in the brain, much of the secondary effect on the heart can be attributed

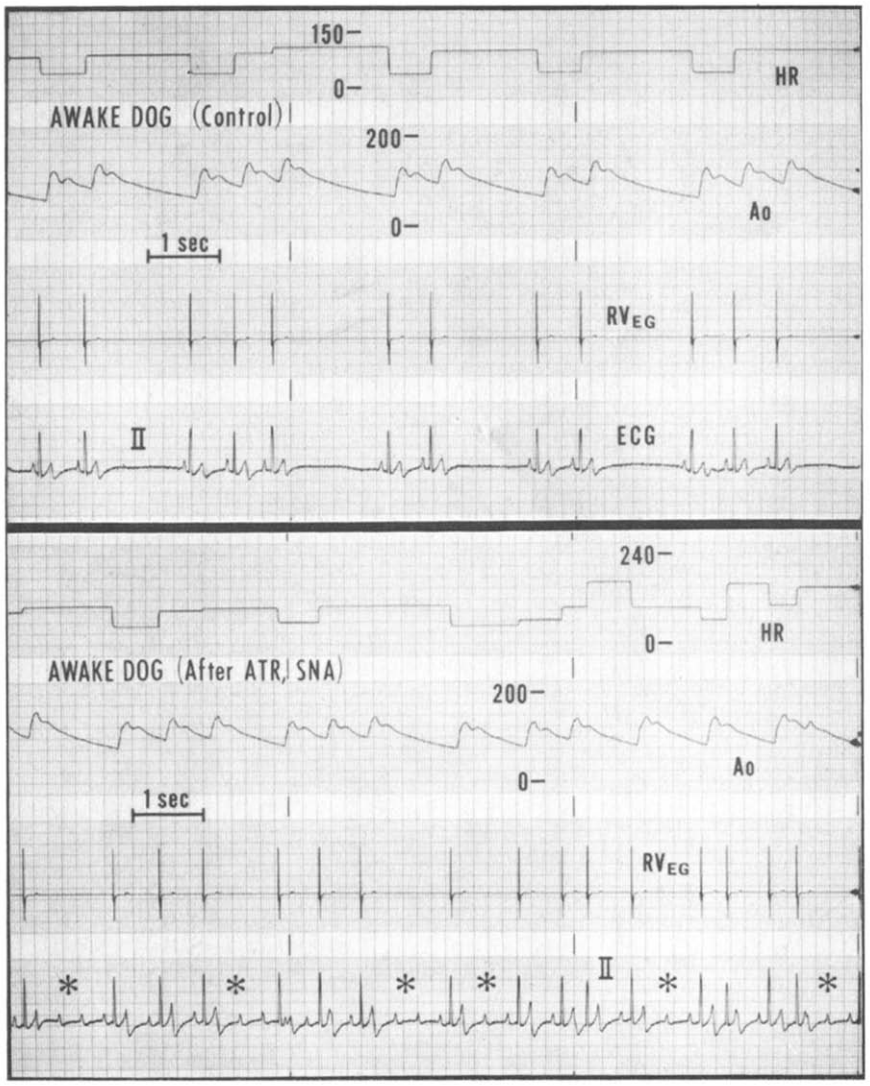


**Figure 8.** These records from a trained unanesthetized dog illustrate sinus arrhythmia (**above**) accompanying spontaneous breathing. **Below**, the normal Hering-Breuer reflex caused phasic heart block (**asterisks**) when the sinus node response was eliminated by atropine (ATR) selectively perfused into the sinus node artery (SNA). Ao = aortic pressure in mm Hg; HR = ventricular rate scaled in beats/min; $RV_{EG}$ = bipolar electrogram from right ventricle. The electrocardiogram is lead II. (Modified from James TN, et al. [27], with permission.)

to distorted efferent neural activity in the heart. If the first event is in the heart, the secondary influence on the brain is most often a result of an abrupt decrease in cardiac output and cerebral perfusion. However, the cardiogenic hypertensive chemoreflex could be an opposite example: a sudden surge of hypertension that causes a peak of cerebral arterial pressure, thus acting as a different type of secondary vascular influence on the brain from the heart.

## AV Junctional Changes and Sudden Death

Within the region of the AV node and His bundle some abnormalities are familiar in form and simple to describe. These include vascular occlusion and ischemic necrosis, as may occur in acute myocardial infarction (35,36), or the development of tumors, which will be discussed later. Slower vascular obstruction can occur in some chronic fibromuscular dysplastic disorders, and when the AV node artery (29) or sinus node artery (30,31) is involved, the impaired nutrition to these electrically specialized centers can lead to slowly progressive degeneration and fibrosis (Fig. 1). But for most readers, the least familiar process affecting AV junctional conduction tissue is the dynamic interplay between this tissue and its neighboring fibrous tissue, which normally abuts and surrounds it.

**Postnatal morphogenesis, and persistent dispersion or fragmentation of the AV node and His bundle.** At about the time of birth, several forms of postnatal molding and shaping begin within and near the heart, as originally discussed by the late Robert Grant (37). These include not only closure of the ductus arteriosus and sealing of the fossa ovalis, but also a sort of "tidying up" or completion in the morphogenesis of the AV node and His bundle (38,39). These two structures appear much larger and more ragged in the human fetus and newborn than they are in the adult human heart, a fact recognized long ago by Keith and Flack (40), who referred to the fetal His bundle as comparatively enormous. For at least the first few months after birth, both

J AM COLL CARDIOL
1983;1:164–83



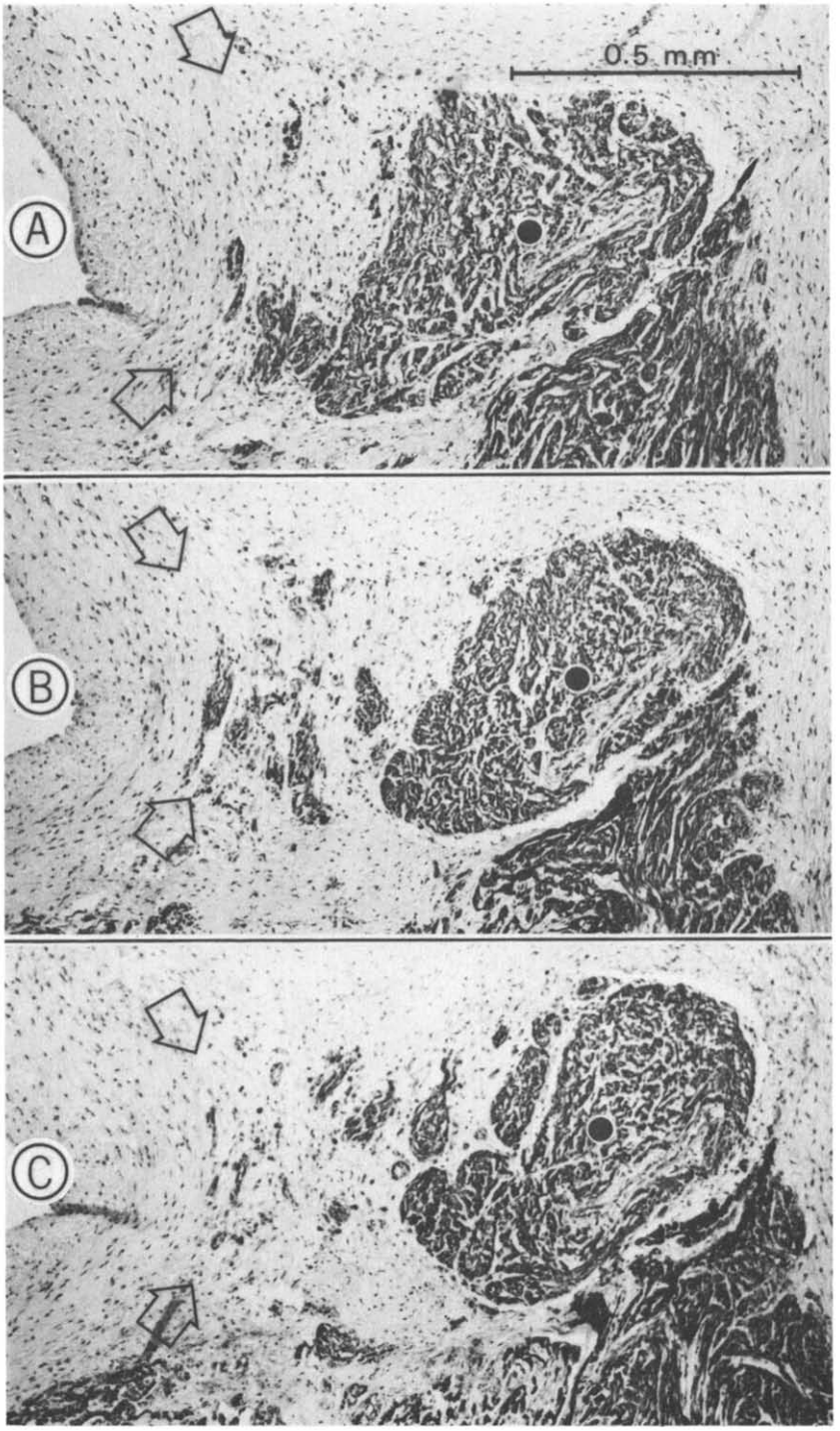


**Figure 9.** Postnatal morphogenesis of the left portion of the His bundle from a 4 month old victim of crib death. These three sections are less than 500 $\mu$ apart. The **black dot** centers the surviving His bundle; the **open arrows** mark the outer margin of resorptive degeneration. See also Figures 10 to 12. (Modified from James TN, et al. [33], with permission.)

the AV node and His bundle exhibit a varying but sometimes large amount of quiet resorptive degeneration (Fig. 9), almost exclusively along the left margin of these two structures. This process is rarely associated with inflammation or overt necrosis or infarction. How it is initiated, why it occurs only on the left side and how it is controlled are completely unknown, but it happens in every human heart. It is thus erroneous to think of it as some sort of abnormality or disease. On the contrary, the absence of this normal postnatal morphogenesis or any marked delay in its completion should be considered abnormal, and this state can be aptly described as persistent fetal dispersion of the AV node or His bundle when observed in adolescence or later in life (Fig. 10). The persistence of such dispersion or frag-

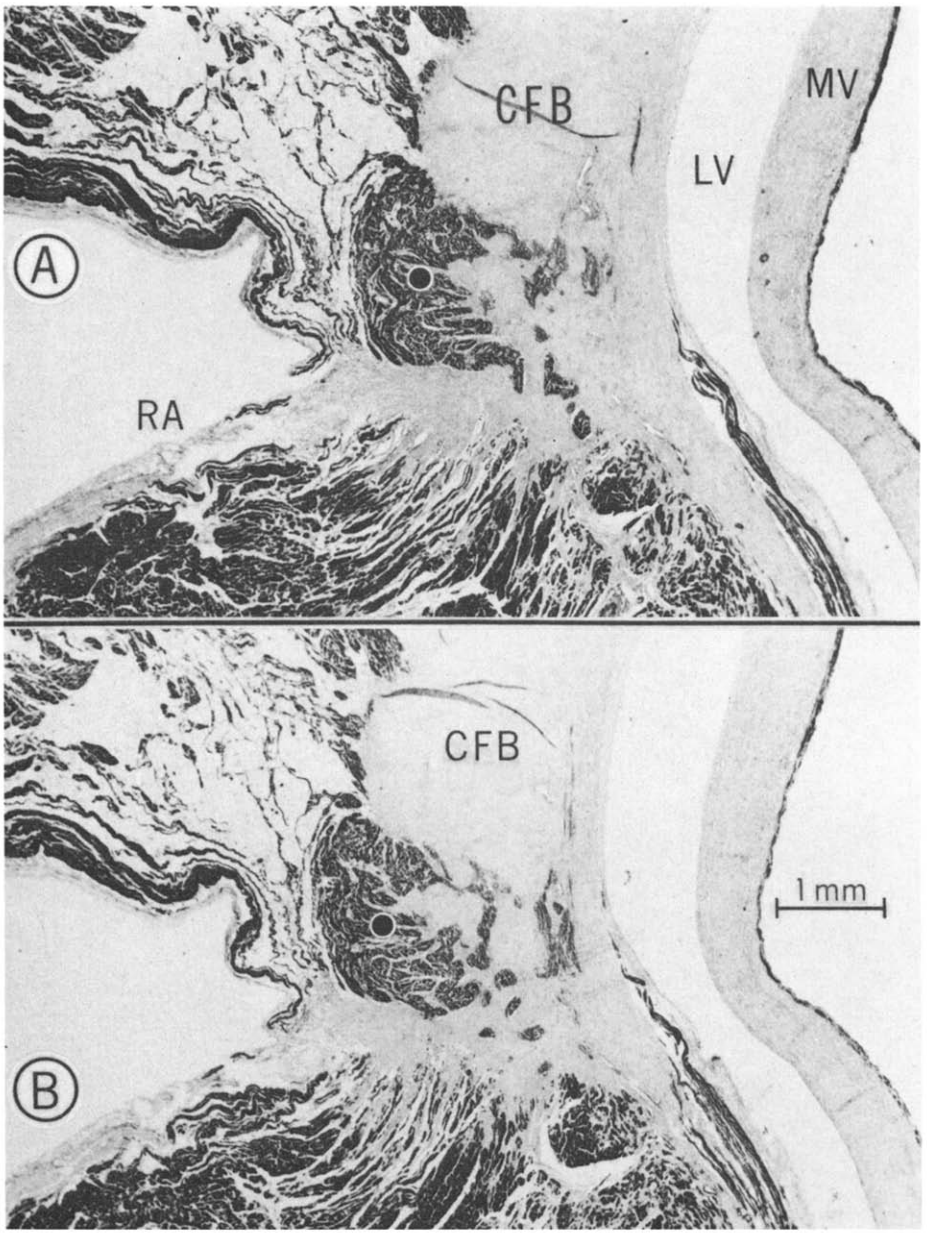


**Figure 10.** Persistent fetal dispersion of the AV node (at the origin of the His bundle) in the heart from a 16 year old victim of sudden unexpected death. **Black dot** marks center of normal AV node, dispersed fragments of which are scattered in the central fibrous body (CFB). LV = left ventricle; MV = mitral valve; RA = right atrium. Photomicrographs are of adjacent histologic sections.

mentation, with abnormal loops and fronds protruding from the AV node or His bundle, could readily be associated with abnormalities in either local automaticity or more likely the provision of an anatomic substrate for reentrant rhythms. It is not surprising, therefore, to find that such a state has been associated with some cases of sudden unexpected death (32).

**Danger of AV junctional malfunction during morphogenesis.** Although postnatal morphogenesis of the AV node and His bundle in human subjects is probably ubiquitous and thus considered a normal process, normal development does not always mean safety. Two additional points concerning this topic merit discussion because they may contribute to an understanding of sudden unexpected death and how important chance becomes in its etiology. The *first* point is the danger of malfunction by the AV node or His bundle at just the time it is being molded or shaped into its eventually safer (probably) and smoother adult form. Many forms of normal morphogenesis are necessarily and regularly associated with cell death, such as the developmental separation of the originally fused fingers of the fetus and the normal opening of the originally imperforate anus. Some portions of the human AV node and His bundle also normally die during their postnatal morphogenesis (Fig. 11). Although it is not possible to know the exact speed and steadiness of progression of the postnatal molding and shaping process, one would expect that it is rather episodic with

J AM COLL CARDIOL
1983;1:164–83



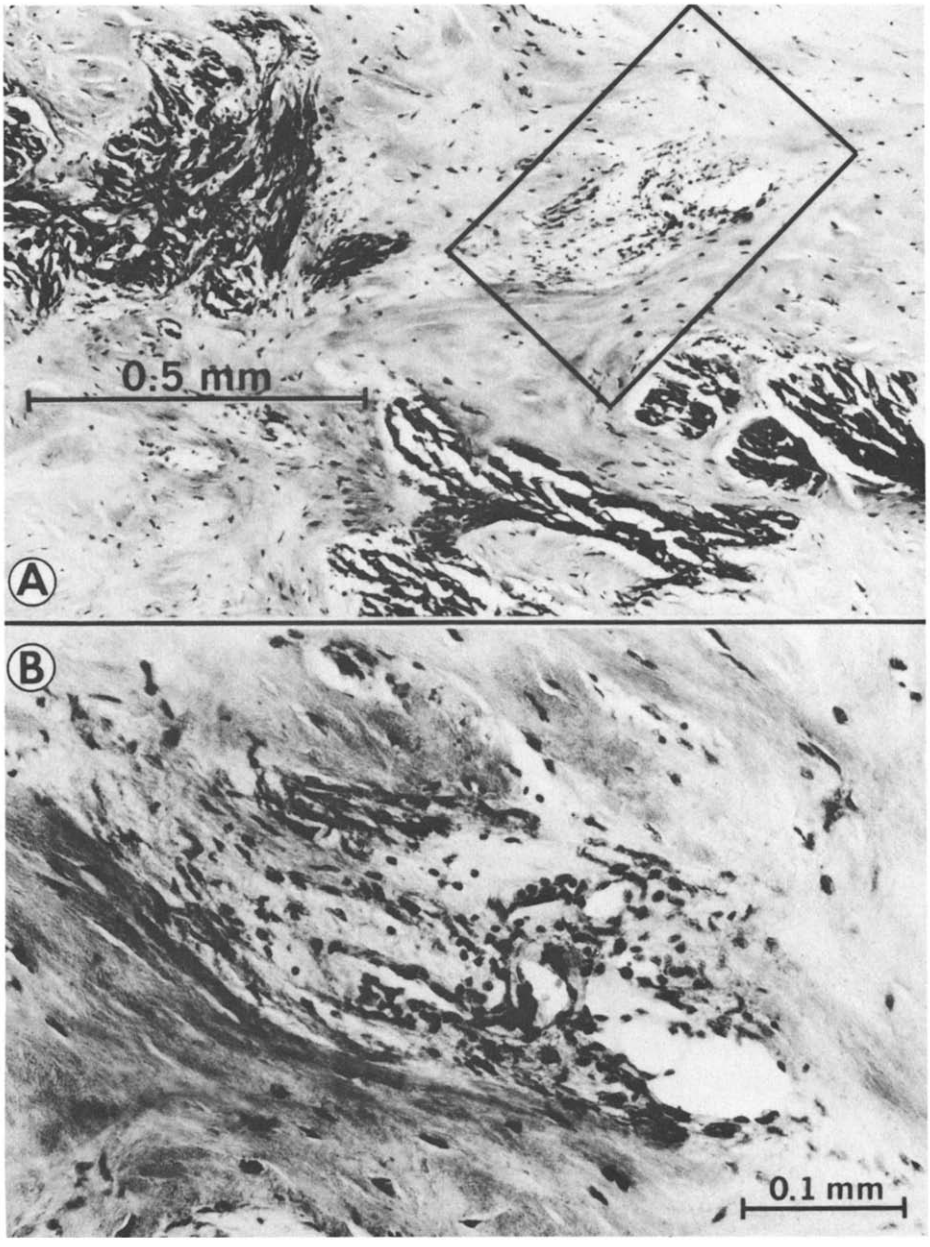


**Figure 11.** Active resorption of one fragment of AV node is boxed within the central fibrous body in **A** and shown at higher magnification in **B**. Same heart as in Figure 10. (Modified from James TN, et al. [6,12,13,29,32,44], by permission of the American Heart Association, Inc.)

waxing and waning of activity and that this varies from one heart to another. Thus, one is not likely to see much of this activity at any given point in time. However, if for some reason the activity were to accelerate so that more conduction tissue was being actively resorbed at any given time, the likelihood of hazardous electrical consequences would increase. Additionally, if during such a surge of activity (or even with lesser activity), other appropriate conditions were present entirely as a result of chance, such as a sudden increase of vagal activity (difficult bowel movement, coughing or vigorous crying), or fever, mild acidosis or toxicity as might occur during a simple viral infection in a baby, then any amount of cell death in the AV node or His bundle could assume much greater significance. This line of reasoning led to the suggestion that lethal electrical instability of the heart may be the final common pathway in crib death (41), even though the originating events or processes could be any of a wide variety of other factors.

**Role of fibroblasts in central fibrous body.** A *second* point concerning the postnatal morphogenesis of the human AV node and His bundle involves the pluripotential nature of the fibroblasts in the central fibrous body that normally abuts or surrounds the conduction tissue. Although we do not know what mechanism controls the nature and degree of activity at the interface between young fibroblasts and cells of the AV node or His bundle, it must be assumed

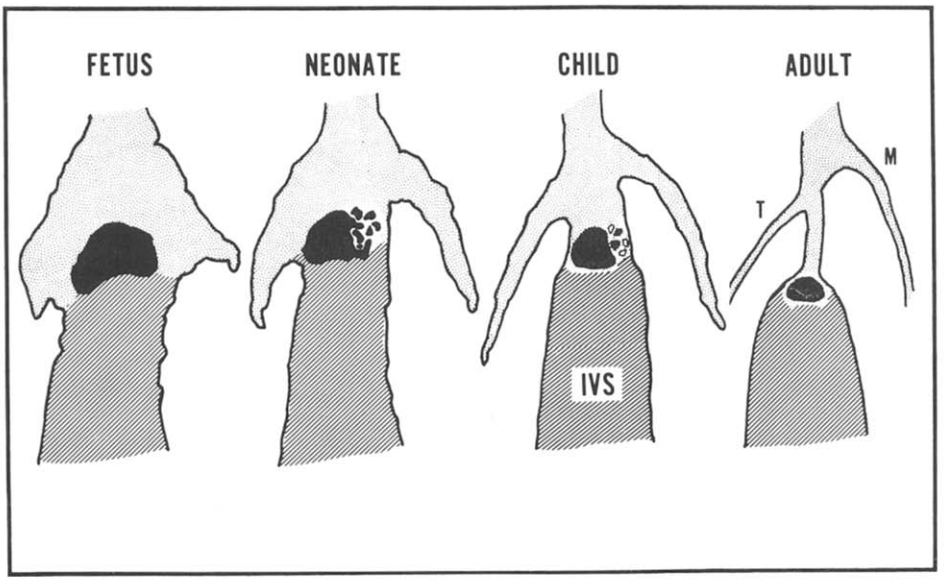


**Figure 12.** Schematic depiction of the normal postnatal morphogenesis of the His bundle. During this period the central fibrous body is transformed from a gelatinous thick mass of young fibroblasts to a dense but thinner wall of collagen. IVS = interventricular septum; M = mitral valve; T = tricuspid valve.

that this important and intricate process is somehow related to cell recognition phenomena, most likely mediated by the biochemical composition of the cell surfaces. In addition to their active participation in the molding and shaping of the AV node and His bundle (Fig. 9 to 12), these fibroblasts sometimes form cysts and lacunae within the central fibrous body (42,43), form fibromatous nodules (27,44) or undergo metaplasia to form cartilage (32) or bone (45). It is not necessary in this discussion to review how any of these misadventures by the fibroblasts could influence the electrical stability within the AV junction. It is sufficient to report that each has been observed to be present in association with sudden unexpected death in human beings or dogs, or both, and that their occurrence and possible influence are additional examples of how chance operates.

## Tumors of the Heart and Sudden Death

Primary and secondary tumors of the heart can be associated with electrical instability, but primary tumors usually cause cardiac enlargement, obstruction or failure, and secondary tumors are usually less important clinically than is the original neoplasm. However, there are three very small primary tumors of the heart that are associated with sudden unexpected death, and it is almost impossible to diagnose them before death with certainty. Because death associated with these primary tumors is often preceded by syncopal episodes, heart block or arrhythmias, such tumors can and should be suspected when no other etiologic explanations are suitable.

*Multifocal Purkinje cell tumors (some of the so-called rhabdomyomas) of the heart are found mainly in children.* Their clinical course is often marked by recurring ventricular arrhythmias that are especially resistant to treatment. Much attention has been directed to the glycogen content of such tumors, but for reasons previously reviewed (46), a more appropriate emphasis may be on their Purkinje cell nature. This is particularly true because they may originate from or disrupt portions of the conduction system, and because the electrophysiologic consequences are unstabilizing.

*A second tumor of the heart sometimes associated with sudden death is fibroma of the central fibrous body (44).* This additional expression of the pluripotential nature of these fibroblasts can lead to nodule formation at any site within the central fibrous body, and this chance-determined location can have quite a different significance depending on where the fibroma forms. If the fibroma is to the left of the His bundle, thus lying just beneath the left ventricular endocardium and accordingly becoming subjected to the highest normal cardiovascular pressure in the body, compression and eventual malfunction of the His bundle may occur (Fig. 13). If the fibroma is higher up in the central fibrous body and is oriented toward the right (Fig. 14), it would then be exposed to the low pressure of the right atrium and, furthermore, be so removed from the His bundle or AV node as to be probably innocuous.

*A third tumor of the heart sometimes associated with sudden death is the benign congenital polycystic tumor of the AV node often called a mesothelioma (47).* Although it has been labeled the smallest tumor causing sudden death (48), one of the paradoxical puzzles about it is that the more usual clinical course is one of many decades of normal life in the presence of incomplete or complete heart block, even though the eventual terminal events can still be sudden and unexpected. A more important practical lesson to be learned from this particular tumor may be that patients with it tolerate electronic pacing poorly. A surprising number of deaths have occurred either during attempted pacing or shortly after

J AM COLL CARDIOL
1983;1:164–83



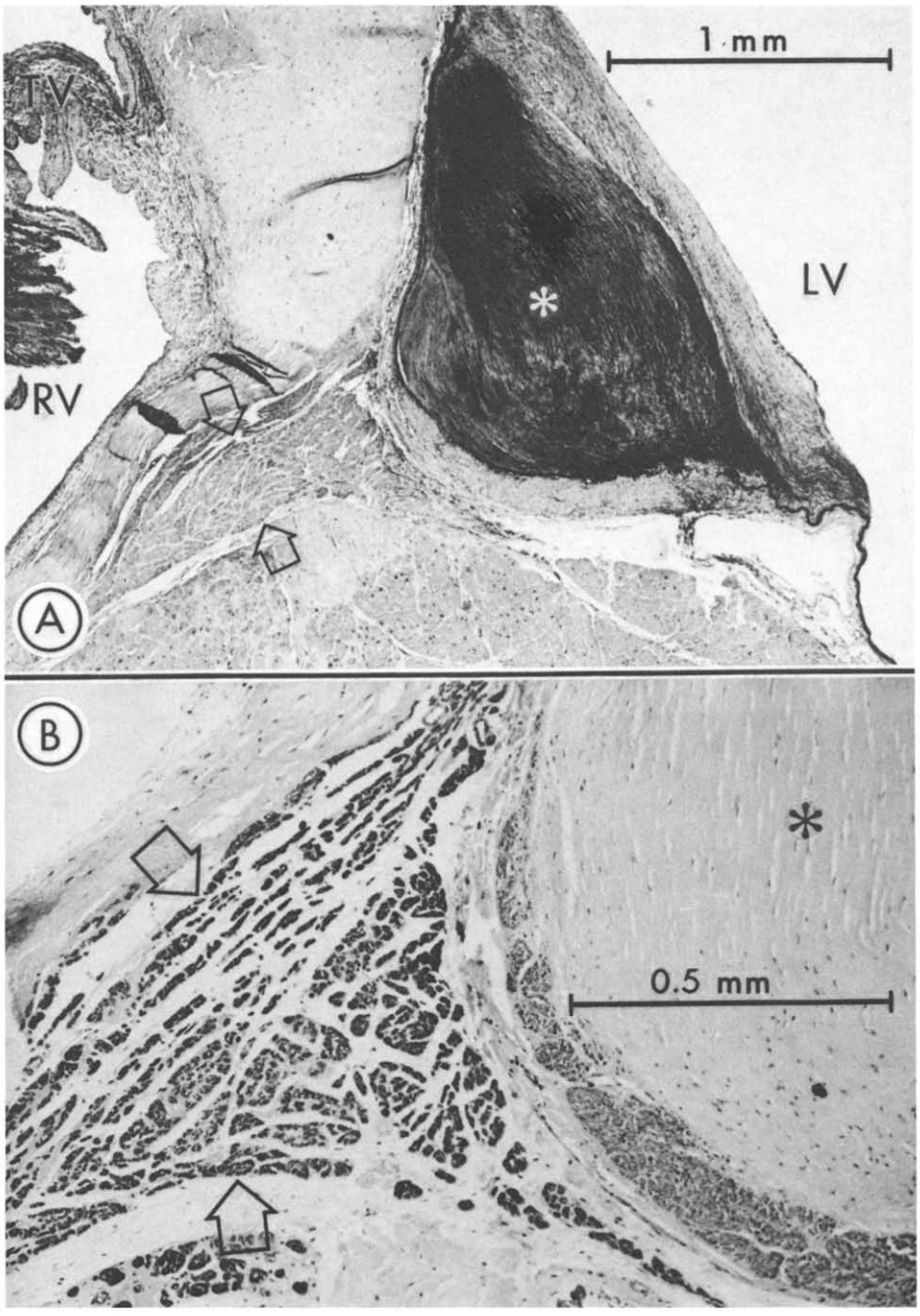


**Figure 13.** Fibroma (**asterisk**) of the central fibrous body compresses the His bundle (**arrows**) which shows reticulated fibrosis in the heart of this middle-aged man who died unexpectedly in his sleep. LV = left ventricle; RV = right ventricle; TV = tricuspid valve. See also Figure 14 (different patient). Verhoeff-van Gieson stain in **A**. (Modified from James TN, et al. [6,12,13, 29,32,44], by permission of the American Heart Association, Inc.)

a pacemaker had been inserted and begun to operate. Because the obvious problem seems to be heart block, difficulty in pacing is something of a paradox. Possible explanations for this paradox are related to the geometrically irregular forward edge of most of these tumors, which rarely enter more than just the proximal margin of the His bundle but virtually destroy the AV node (Fig. 15), or to some other factor that fragments the electrical signal from the pacemaker in some unknown lethal way.

## Ventricular Fibrillation and Sudden Death

Clinical lore teaches that most examples of sudden unexpected death are due to ventricular fibrillation. Although this may be true, for more effective prevention it is more useful to understand better the predisposing and fundamentally responsible processes or mechanisms. Thus, the determination of ventricular fibrillation threshold in an experimental animal, and the subsequent testing of procedures

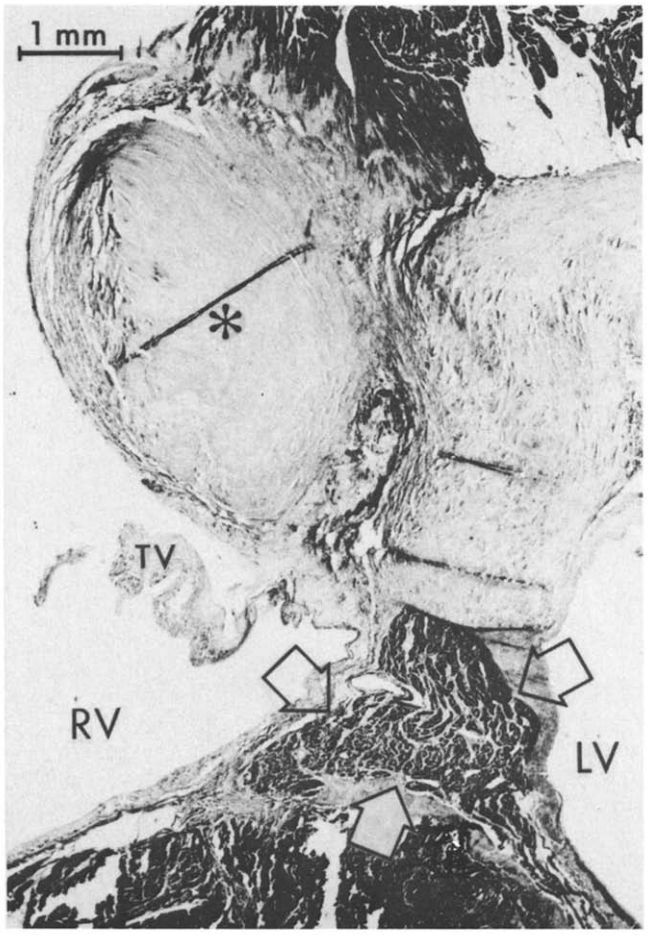


**Figure 14.** This fibroma of the central fibrous body protrudes into the low pressure right atrium (RA), is also located some distance away from the normal-appearing His bundle (**arrows**), and is consequently unlikely to be functionally significant.

LV = left ventricle; RV = right ventricle; TV = tricuspid valve. (Modified from James TN [38], with permission.)

or medications that could alter the threshold, may have only tenuous relevance or none at all in the context of sudden death in human subjects. It is essential to remember that ventricular fibrillation in human beings can be transient (with or without treatment), although no one would advocate waiting to see whether it stops if untreated. Ventricular fibrillation may also be the terminal event only, having been preceded by a wide assortment of more readily treatable electrophysiologic abnormalities. In most examples of human ventricular fibrillation, it is highly probable that the origin was multifactorial, that the cause of one episode may be quite different from that of a preceding or subsequent episode and that in different patients the cause is unlikely to be the same or necessarily even similar in nature.

*For the sake of illustrating how chance contributes to the onset of ventricular fibrillation,* consider that the precipitating factor might be transient embolic platelet showers, small elements of debris from a rupturing atheroma, any of several powerful reflexes or emotional stress, temporarily altered ventricular repolarization or coronary spasm. Each of these can be as evanescent as it can be devastating, and each can occur superimposed on some otherwise innocuous anatomic variation or abnormality in the heart. Two such anatomic factors that may especially render transient ventricular fibrillation more apt to become sustained are focal fibrosis (of any origin) or marked hypertrophy of the left ventricular myocardium.

## General Comment

Chance and sudden death relate to each other in both a horizontal and vertical fashion, forming a morbid matrix of concurrence versus sequence. Horizontal chance is represented by the largely unpredictable concurrence of different influential events or processes at any one time. The sequence of events that appear and perhaps disappear in the subsequent passage of time is an example of vertical chance. The essential lesson is an appreciation of the wide diversity of these factors and their unpredictable variability in the pathogenesis of sudden unexpected death.

*Ventricular premature beats are the subject of many investigations dealing with sudden death,* and their prevention has become an almost obsessive concern of some researchers. Premature beats are indeed an appealingly simple marker event, and they do lend themselves to a wide assortment of classifications, enumerations and attempted modifications. It is well to remember that they are also very often harmless. Harm arises with certain intrinsic features of the premature beats themselves, such as close coupling intervals or multiple and multiform QRS complexes. Harm is also probably more significantly associated with the presence of focal myocardial ischemia, ventricular hypertrophy, marked abnormality of blood pressure (very high or very low) or concomitant abnormality of heart rate or rhythm, including marked bradycardia, tachycardia or heart block. How many of these compounding influences coexist with the premature beats at any given time is often a matter of chance.

*If it is assumed that one or more unusual factors can randomly aggregate to cause sudden unexpected death,* then we must ask how often do any or several of these same factors also contribute to, or actually cause or become essential for, sudden death of an ostensibly "known" cause, such as coronary disease, myocardial infarction or pulmonary embolism. Although we readily accept many of these findings as adequate explanations of sudden death, the outcome might not have been lethal except for the coexisting presence of some less obvious but crucial element in a summation process. As a corollary, the selection of suitable "control" observations for research into sudden death then becomes a more complex problem than most realize.

J AM COLL CARDIOL
1983;1:164–83



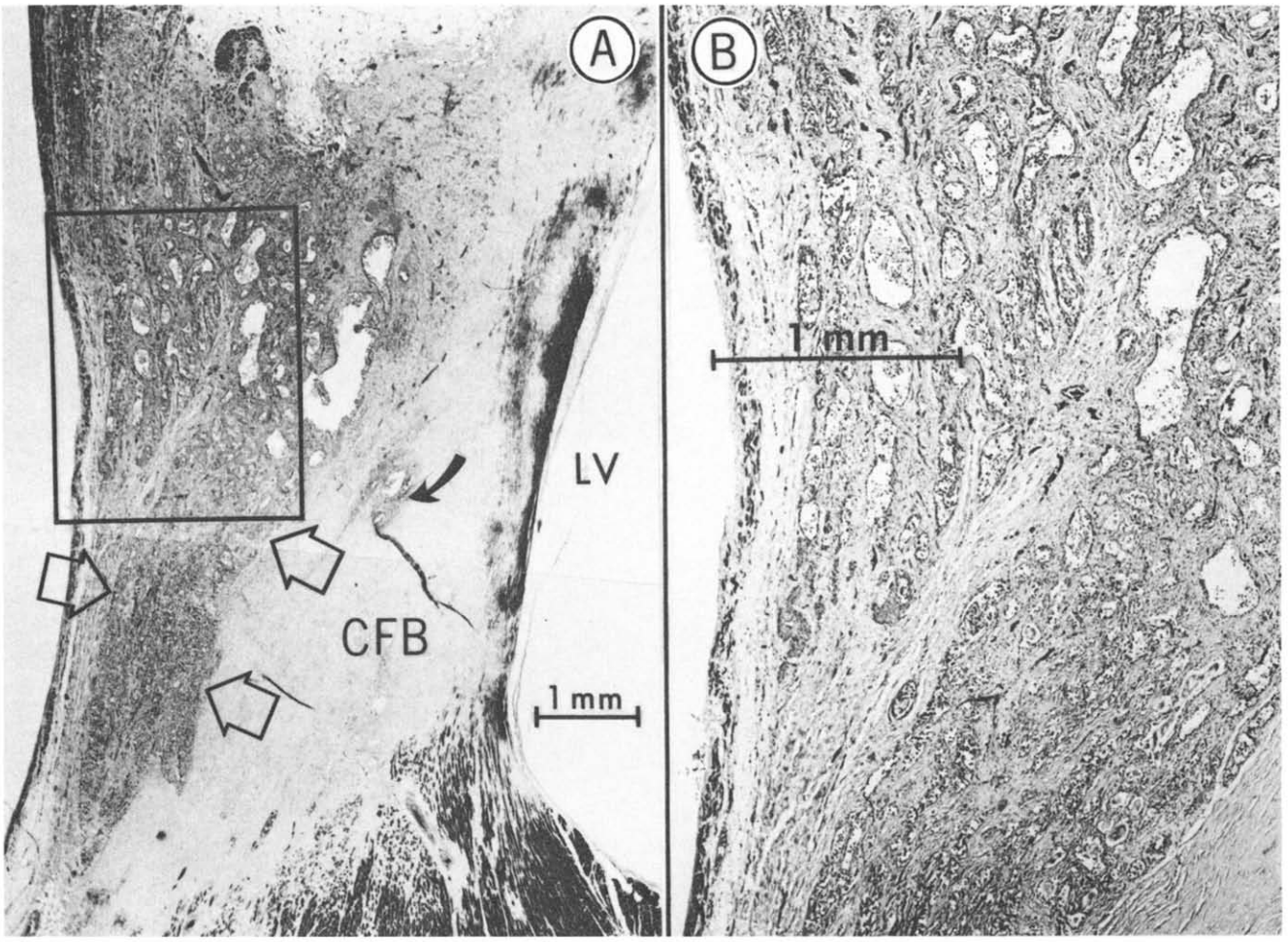


**Figure 15.** Benign congenital polycystic tumor destroys the AV node (**arrows** in **A**) of this patient who died with heart block. A fragment of tumor is marked with a **curved arrow** in the central fibrous body (CFB) in **A**. The **boxed area** in **A** is seen at higher magnification in **B**. (Modified from James TN, et al. [6,12,13,29,32,44], by permission of the American Heart Association, Inc.)

*It is useful to understand that some of the randomly determined factors contributing to the likelihood of sudden unexpected death can be recognized during life,* but it is equally important to know that some of them cannot be recognized. Some factors are susceptible to available types of treatment or modification and others are not. For example, smoking, excessive worry, obesity, temporary hypoxia or acidosis can each be treated, sometimes readily and at other times with great difficulty. On the other hand, recognizing and treating a tiny fibroma compressing the His bundle (44) may not ever be possible, and the same can be said of persistent fetal dispersion of the AV node or His bundle (32). If transient heart block or episodes of reentrant tachycardia are the functional consequence of either of these two "untreatable" lesions, then their electrophysiologic manifestations can be treated; however, this is not the same as eliminating the fundamental problem.

*For the production of cardiac electrical instability there is causative interplay between many different intracardiac and extracardiac factors.* Within the heart the specific blood supply to either the sinus node or the AV junction may fail for a variety of reasons. Focal ischemia can additionally occur in many other locations within the myocardium and in some places would elicit certain neuroreflexes. Serotonin released by aggregating platelets at specific sites within the coronary circulation can cause a powerful hypertensive reflex (6–10). Transient obstruction (platelets, coronary spasm) can combine with or occur without prior presence of fixed coronary narrowings. Outside the heart, factors that can influence its electrical performance include emotional processes such as fear, anxiety or depression, somatic expressions such as debility, hypoxia, acidosis, fever or anemia and circulating substances such as cardioactive ions, catecholamines or prescribed medications. Although many of these factors considered alone seem innocuous (or even beneficial) and unlikely to cause sudden death, a mild fever

or hypoxia often encountered in epidemic pulmonary infections may be the only additional element required to unbalance the performance of the conduction system. The simple vagal reflex that must be anticipated as a normal response to events as mundane as coughing, sneezing or laughing also could be the single other factor needed to precipitate a lethal arrhythmia.

*What can best be done to improve our understanding of sudden death and thereby develop more effective ways to prevent it?* Recognition of the random or chance nature of the aggregation of the many responsible components in the etiology of sudden death is an important first step. With any of these components allowance must be made for individual variability and for the transient nature of many of these etiologic factors, including some of the most influential ones. Neither the occurrence nor the concomitance of most of these factors is very predictable, and many are undetectable.

*Sudden death from electrical instability of the heart is rarely caused by a single factor.* Of the multiple factors that may contribute, some will be sequential in nature; others occur concomitantly and may be significant only when occurring at the same time as other factors. Some factors (hypoxia, anemia and fever) are readily reversible or treatable; others (congenital or acquired structural abnormalities in or around the conduction system) cannot be reversed or changed. It is not enough to recognize that some form of electrical instability can be the terminal event, because the ventricular fibrillation that does not spontaneously revert may differ little or not at all—at least in its intrinsic electrophysiologic features—from that which is transient.

*The great majority of victims of sudden death have coronary disease, usually extensive in nature.* However, none developed that coronary disease in a short period of time, but over the course of many years. Two useful questions in understanding why such people die suddenly and expectedly are 1) What was different in that person at the time of sudden death? 2) Remembering the multifactorial etiologic factors previously discussed, which of these may have coexisted at the fatal moment in the subject who has long had coronary disease? Concerning the latter question, there is little reason to expect that persons with severe coronary disease have any protection from any of these noncoronary factors.

*Finally, in recognizing that sudden death and severe coronary disease often coexist in men of middle age or older, we must not lose sight of the wealth of information to be had from other forms of sudden death in which coronary disease plays little or no role.* Examples include sudden death that occurs in babies, young athletes, the grief-stricken of any age, hex victims, persons with a long QT interval (with or without deafness) and even others. Rather than concluding that in these noncoronary examples the pathogenesis of sudden death is quite different, we should more properly be concerned with whether the pathogenesis of sudden death in coronary disease had much to do with the coronary disease itself. In any of these categories the likelihood of preventing sudden unexpected death will improve only when all components of the pathogenesis receive due consideration. From postmortem examinations a good beginning would be to make the special study of the conduction system with its blood supply and innervation an indispensable practice, because at the very least one should know the morbid appearance of those structures primarily responsible for electrical impulse formation and conduction in the heart.

> Nature is not only queerer than we suppose, she is queerer than we can ever suppose.
> G. B. S. Haldane
>
> Nature will lie to you every way she can.
> Charles Darwin

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This review is adapted (modified) from one originally prepared for *Progress in Cardiology* (49).

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