HISTORY

History of Wolff-Parkinson-White Syndrome
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SCHEINMAN, M.: History of Wolff-Parkinson-White Syndrome. While Drs. Wolff, Parkinson, and White fully described the syndrome that bears their names in 1930, prior case reports had already described the essentials. Over the ensuing century this syndrome has captivated the interest of anatomists, clinical cardiologists, and cardiac surgeons. Stanley Kent described lateral muscular connections over the atrioventricular (AV) groove, which he felt were the normal AV connections. The normal AV connections were, however, clearly described by His and Tawara. True right-sided AV connections were initially described by Wood et al., while Öhnell first described left free wall pathways. David Scherf is thought to be the first to describe our current understanding of the pathogenesis of the Wolff-Parkinson-White (WPW) syndrome in terms of a reentrant circuit involving both the AV node—His axis as well as the accessory pathway. This hypothesis was not universally accepted and many theories were applied to explain the clinical findings. The basics of our understandings were established by the brilliant work of Pick, Langendorf, and Katz who by using careful deductive analysis of ECGs were able to define the basic pathophysiological processes. Subsequently, Wellens and Durrer applied invasive electrical stimulation to the heart in order to confirm the pathophysiological processes. Sealy and his colleagues at Duke University Medical Center were the first to successfully surgically divide an accessory pathway and ushered in the modern area for curative therapy for these patients. Morady and Scheinman were the first to successfully ablate an accessory pathway (posteroseptal) using high-energy direct-current shocks. Subsequently, Jackman, Kuck, Morady, and a number of groups proved the remarkable safety and efficiency of catheter ablation for pathways in all locations using radiofrequency energy. More recently, Gallob et al. first described the gene responsible for a familial form of WPW. The current ability to cure patients with WPW is due to the splendid contributions of individuals from diverse disciplines from throughout the world. (PACE 2005; 28:152–156)

historical review, Wolff-Parkinson-White syndrome, catheter ablation, cardiac electrosurgery, preexcitation, accessory pathways

Evolution of the Wolff-Parkinson-White Story
The Wolff-Parkinson-White (WPW) syndrome holds particular interest not only for clinical cardiologists but also for anatomists, surgeons as well as clinical and experimental electrophysiologists. This syndrome focused the efforts of myriads of workers from a variety of disciplines and was dependent upon a clear knowledge of both the normal conducting system as well as mechanism of reentrant arrhythmias.

We shall start our story with the first complete description of the syndrome, which was published in the American Heart Journal in August 1930.1 Drs. Wolff, Parkinson, and White described 11 patients without structural cardiac disease who had a short P-R interval, “bundle-branch block” and paroxysmal supraventricular tachycardia and/or atrial fibrillation. They made particular note of the fact that use of atropine or exercise would tend to normalize the ECG while increases in vagal tone did the opposite. They felt that the arrhythmias were due to “associated nervous control of the heart.” In their report they credited Dr. F.N. Wilson who described the identical findings in a single case (1915)2 and Dr. A.M. Wedd3 in 1921.

Anatomic Findings
At the time of the initial observations, it was appreciated that the atrium and ventricles were electrically linked via the atroventricular (AV) node and His bundle. In addition, the bundle branches and the Purkinje system had been described and the electrocardiographic pattern of
bundle-branch block had been identified.\textsuperscript{4—6} It is, therefore, clear why the early clinicians categorized ventricular preexcitation as a bundle-branch block phenomenon.

We now need to digress a bit and relate to the work of the anatomists in the late 19th and early 20th centuries. It was appreciated that electrical connections bridged the atrium and ventricles in mammalian hearts\textsuperscript{7,8} and the nature of these connections were of great interest. Stanley Kent\textsuperscript{9} in 1893 found lateral AV connections and thought these constituted the normal AV-conduction system in man. This work proved controversial and was, in fact, rejected by Sir Thomas Lewis as well as by Drs. Keith and Flack. In contrast, the work of His\textsuperscript{10} and Tawara\textsuperscript{11} clearly defined the normal AV-conducting system. Of interest was a later study by Kent—describing a lateral AV connection and a node-like structure within the connection.\textsuperscript{12} While some have interpreted this finding as the first description of a right atriofascicular tract, but it should be appreciated that Kent felt that this structure was part of the normal AV-conduction system. It is indeed odd that Kent is given credit for first describing accessory extranodal AV pathways since that credit clearly belongs to others; neither should he be properly credited with the first description of atriofascicular pathways.

In contrast, Wood et al.\textsuperscript{13} deserve credit for the first description of a right-sided extranodal accessory pathway (1943) and Öhnell\textsuperscript{14} found the first left lateral pathway (1944). Other important contributions included the work of Mahaim,\textsuperscript{15} who described connections between the AV node or His bundle to the fascicles or ventricular muscle. Lev both found that Mahaim\textsuperscript{16} tracts could produce a pattern of preexcitation and nicely consolidated our modern understanding of the normal conduction system.\textsuperscript{17} In a landmark study, Lev and Lerner presented detailed anatomic studies of 33 fetal and neonatal hearts.\textsuperscript{17} They concluded that: no accessory pathways normally existed outside the AV-conduction system; structures considered by Kent to be nodes were actually insertions of atrial muscle; and that in fetal or neonatal hearts there are sparse development of collagen and hence there was close proximity, but no communication between the atrium and ventricle.

**Evolution of Theories to Explain Ventricular Preexcitation and Tachycardia**

The early clinicians were focused on the “vagal” effects on the preexcitation pattern and invoked vague neuro-cardiac mechanisms to explain associated arrhythmias. The concept of reciprocal rhythms were well established and it was Mines, who in fact, postulated a reciprocal rhythm involving the AV node and accessory pathway.\textsuperscript{18} According to TN James,\textsuperscript{19} Holzmann and Scherf\textsuperscript{20} in 1952 were the first to describe preexcitation as being due to an extranodal accessory pathway. Similar conclusions were made by Wolferth and Wood\textsuperscript{21} who labeled this pathway as “bundle of Kent.”

These findings were not, however, generally accepted and lead to a profusion of alternative ideas. For example, Hunter et al.\textsuperscript{22} felt that the syndrome was due to a fusion of pacemakers (sinus conducted complexes and a pacemaker from the bundle branches). Printzmetal\textsuperscript{23} (1952) attributed the findings to accelerated AV conduction with pathways around the node. Sodi-Pallares (1952) invoked “hyperexcitability of the right side of the septum.”\textsuperscript{24}

The seminal work by Butterworth and Poindexter\textsuperscript{25} in 1942 clearly demonstrated that an artificial connection between the atrium and ventricle could mimic classic preexcitation and led to the acceptance of an extranodal pathway as the cause for preexcitation. Pick, Langendorf, and Katz made enormous contributions to our understandings of this syndrome.\textsuperscript{26—28} They noted some 60 theories used to explain preexcitation but felt that only the presence of extranodal accessory pathway could explain all their findings. By detailed and painstaking deductive analyses of literally thousands of ECGs, they amazingly described variations in the nodal versus pathway refractoriness as a mechanism for initiation of paroxysmal supraventricular tachycardia. They elucidated the relationship between paroxysmal tachycardia and atrial fibrillation and distinguished extranodal from AV-nodal pathways. Their incredible insights heavily influenced subsequent human cardiac electrophysiologic studies.

**Clinical Electrophysiologic Examination**

Drs. Durrer and Wellens\textsuperscript{29,30} were the first to systematically use programmed electrical stimulation of the heart in order to better define the mechanism(s) of arrhythmias. It should be emphasized that their observation antedated the recording of His bundle activity in humans.\textsuperscript{31} The Dutch group showed that reciprocating tachycardia could be induced by premature atrial or ventricular stimulation; that the tachycardia could be either orthodromic or antidromic, and defined the relationship of the accessory pathway refractory period to the ventricular response during atrial fibrillation. These workers provided the framework for use of intracardiac studies to define location and physiology of these pathways.\textsuperscript{32,33} Current understanding of the types of accessory pathways are detailed in Figure 1.
The myriad types of accessory connections are detailed in this figure. The so-called Kent fibers are extranodal pathways and are the most common of the atrioventricular pathways. Accessory AV-nodal bypass tracts may either insert into the fascicles and are also commonly called Mahaim fibers. More accurately, Mahaim fibers connect the node or fascicles to the ventricles. These twigs are not involved in the genesis of arrhythmias. Figure supplied courtesy of Dr. John D. Fisher.

Cardiac-Surgical Contribution

Prior to the era of catheter ablation, patients with supraventricular arrhythmias that were refractory to medical therapy underwent direct surgical ablation of the AV junction. This approach would, however, not be appropriate for the management of the patient with atrial fibrillation with rapid conduction over a bypass tract. Durrrer and Roos (1967) were the first to perform intraoperative mapping and cooling to locate a right free wall accessory pathway. Burchell et al. used intraoperative mapping to locate a right sided pathway and showed that preexcitation could be abolished by injection of procainamide (1967). A limited surgical incision over this area resulted in only transient loss of preexcitation. Sealy and the Duke team were the first to successfully ablate a right free wall pathway (1968). They initially used an epicardial approach. Their subsequent amazing results conclusively showed that the vast majority of WPW patients could be cured by either direct surgical or cryoablation of these pathways. Iwa from Japan concurrently demonstrated the effectiveness of cardiac electrosurgery for these patients. He is credited with being the first to use an endocardial approach for pathway ablation. The endocardial approach was subsequently independently used by the Duke team of Sealy and Cox. Only later was the “closed” epicardial approach reintroduced by Guiraudon.

Catheter Ablation

The technique of catheter ablation of the AV junction was introduced by Scheinman et al. in 1981. The initial attempts used high energy direct current countershocks to destroy cardiac tissue and hence expansion of its use to other arrhythmias was limited. Fisher et al. (1984) attempted to ablate left sided accessory pathways through the coronary sinus. This technique was abandoned due to limited efficacy and a high incidence of cardiac tamponade. Morady and Scheinman (1984) introduced a catheter technique for disruption of posteroseptal accessory pathways. This was associated with a 65% efficacy and cardiac tamponade could be avoided by shock delivery outside the coronary sinus. Warin et al. described successful ablation of nonseptal pathways.

The introduction of RF energy in the late 1980s completely altered catheter ablative procedures. The salient advances in addition to RF energy included much better catheter design, together with the demonstration that pathway localization could be facilitated by direct recording...
of the pathway potential. The remarkable work of Jackman et al.,47 Kuck et al.,48 and Calkins49 ushered in the modern era of ablative therapy for patients with accessory pathways in all locations. Moreover, a variety of registry and prospective studies have documented the safety and efficacy of ablative procedures for these patients.30,31

The Future

At this point of time, catheter ablation procedures are approaching the apotheosis of its success while future developments in catheter design, alternative energy sources (e.g., cryoablation), and advanced imaging will lead to improvements. These advances will be largely incremental. Clearly, the future major advances belong in the realm of better understanding of the molecular genetics and basic pathophysiologic processes that produce this syndrome. Mehdirad et al.52 described an autosomal dominant form of WPW associated with cardiomyopathy and progressive conduction system disease linked to chromosome 7q3. Recently, Gollob et al.53 successfully identified a gene responsible for the WPW syndrome. They identified two separate families with the same genetic abnormality. Of interest were the unusual clinical features which included an approximately 40% incidence of atrial fibrillation and/or flutter, a high incidence of pathways with decremental conduction, ventricular hypertrophy, sinus node abnormalities, and sudden death. They identified a missense mutation in the gene that encodes the gamma-2 regulatory subunit of AMP activated protein kinase. Protein kinase is involved in phosphorylation of many downstream substrates. The exact link between this genetic abnormality and the genesis of the WPW syndrome is not known. How this and other genes control cardiac morphogenesis is a great challenge for future understanding of the development of these aberrant pathways.

Conclusion

The WPW story at this stage has culminated in a rather remarkable situation that allows for ready cure of the vast majority of our patients. We now appreciate that the current situation could not have been achieved without the remarkable clinical acumen of our predecessors, painstaking work of the anatomists, together with the ingenuity and skills of the clinical electrophysiologists and cardiac surgeons. Happily, we have not reached the final chapter of this remarkable story. I think the next major advances belong to the molecular biologists to help unravel the basic genetic flaw(s) in the WPW syndrome.

Acknowledgment: This article was written at the invitation of Dr. Sy Furman. Sy is an individual for whom I hold the greatest respect and admiration. His love for history of medicine is well known. I thank him for transfecting his enthusiasm to me.

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