

## From Teare to the Present Day: A Fifty Year Odyssey in Hypertrophic Cardiomyopathy, a Paradigm for the Logic of the Discovery Process

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This year marks the fiftieth anniversary of the first contemporary account of hypertrophic cardiomyopathy by Dr Robert Donald Teare, a pathologist working at St George's hospital in London. In a now seminal case series in the *British Heart Journal*, Teare reported asymmetric hypertrophy of the interventricular septum in 8 patients between the ages of 14 and 44.<sup>1</sup> Although widely recognised as a citation classic, Teare's observations were not the earliest historical description of hypertrophic cardiomyopathy. Evolution of the current perspective on the disease can be traced from antiquity through the ages. Philosophers and science historians have expounded the view that discoveries per se are often fortuitous; logic comes into play in proving that the finding is a bona fide discovery, or in cultivating a novel paradigm from the discovery. In their 1977 dissertation on the nature of scientific discovery, Howard and Allan Adelman set forth the premise that logic is inherent to the discovery process itself, using a case study of hypertrophic cardiomyopathy<sup>2</sup> as their primary example.

References to sudden cardiac death are found in the 2400-year old *Aphorisms of Hippocrates*.<sup>3</sup> In the seventeenth and eighteenth centuries, Theophile Bonet, John Baptiste Morgagni, William Harvey, and Giovanni Maria Lancisi variously reported enlarged hearts with increased muscle bulk, obstruction of blood flow from the left ventricle into the aorta, hypertrophy, degenerative changes, and fibrosis.<sup>4</sup> Tentative connections were drawn between the anatomical findings, sudden death, and antecedent history, including chest pain, palpitation, and "swooning" (syncope). Two French pathologists, Hallepeau and Liouville, described the classic appearance of asymmetrical hypertrophy of the interventricular

septum in 1869.<sup>5,6</sup> Recognition that this phenomenon was a primary myocardial disorder came from Krehl<sup>7</sup> in 1891.

In the year preceding publication of Teare's account, Dr Paul Wood of the National Heart Hospital described in a letter a condition he called functional muscular subvalvar aortic stenosis due to gross hypertrophy of the outflow tract. Paul Wood had neither the benefit of non-invasive imaging techniques, nor a surgeon's view of the in vivo heart, nor even access to morbid anatomy. He deduced the nature of the disorder based solely on his findings on clinical examination: a jerky pulse, double apex beat, and ejection systolic murmur. He continued: "for reasons still difficult though, we do not understand how the muscle gets so thick that it tends to obstruct and cause the outflow tract murmur and thrill... To elucidate the nature of this obstruction I would hesitate to use sympathometric agents; they may well be dangerous and any manoeuvre which alters afterload or preload however may be instructive." His ability to infer the underlying physiology from the physical signs he elicited was considered prodigious at the time; in our current era of declining examination skills, it seems nothing short of miraculous.<sup>8-10</sup>

Contemporaneously, Sir Russell Brock, a surgeon at Guy's Hospital, reported 3 patients with subaortic outflow obstruction in the setting of concentric left ventricular hypertrophy, effectively inoperable before the advent of cardiopulmonary bypass.<sup>11,12</sup> Brock's findings supported the notion that left ventricular outflow tract obstruction could arise as a consequence of ventricular hypertrophy, and underscored the importance of distinguishing between aortic stenosis and obstruction at the subvalvular level.

The Adelmans proposed 4 stages through which medical discoveries are conceived and developed.<sup>2</sup> In stage I, the anatomical abnormality is recognised as novel, and linked with specific physiological features. Subsequently, the clinical, pathological, and physiological findings and an ostensible cause must be shown to coexist within the same entity. In their rational reconstruction of the discovery of hypertrophic cardiomyopathy, the Adelmans contended that Brock's exposé was the culmination of this preliminary phase. The Adelmans'

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second stage is distinguished by the uncovering of evidence that conflicts with the interpretations of the original discoverer, without undermining the validity of the discovery, and the inability of novel conceptions of the disease to fit all the empirical evidence, although each represents a key piece of the final puzzle.<sup>2</sup> Teare's account was considered by the Adelmans to herald the second phase of the discovery process, but also served as the bridge between the 2 chapters in the history of the disease.

Donald Teare's achievement was distinct from his predecessors and contemporaries, and unique in its advancement of our understanding of hypertrophic cardiomyopathy. In a single communication, he presented most of the cardinal features of the disease. Antemortem symptoms in the cases described included chest pain, palpitation, syncope, and exertional dyspnoea. The electrocardiographic findings of T-wave inversion and pathological Q-waves were documented. Seven of the 8 patients in the series died suddenly. While a pathological study, by its very nature, cannot offer a representative view of the incidence of fatal complications, it drew attention to what remains the most devastating outcome of the disease: premature sudden death. In community-based cohorts without tertiary centre referral bias, the annual incidence of sudden death from hypertrophic cardiomyopathy is 0.7%-1%,<sup>13,14</sup> but much of the clinical management of hypertrophic cardiomyopathy remains geared towards identifying the at-risk minority. Three patients had atrial fibrillation, which is now known to affect at least 20%-25% of patients with hypertrophic cardiomyopathy, and confer a significant risk of thromboembolism.<sup>15</sup> One of the patients in Teare's series suffered a cerebral embolism at the age of nineteen, following the onset of atrial fibrillation.<sup>1</sup> Thus, in an 8-case series, Teare succeeded in highlighting most of the major clinical complications of the disease. Yet perhaps the most significant contribution to posterity was the unified portrayal of the pathological profile of hypertrophic cardiomyopathy: unexplained hypertrophy of the left ventricle, with right ventricular involvement in 2 cases; and muscle bundles in different orientations separated by connective tissue on histology.<sup>1</sup> Myocyte disarray remains the most pathognomonic feature of hypertrophic cardiomyopathy. With remarkable insight, Teare commented that "the fibrosis evident in certain cases is ischaemic in type."<sup>1</sup> Ischaemia is now recognised as a central to the pathogenesis of hypertrophic cardiomyopathy, a key cause of the characteristic chest pain, and a probable trigger for arrhythmia, particularly when superimposed on a substrate of myocyte disarray and fibrosis.

In an addendum at the end of his paper, Donald Teare reported the sudden death of the 16-year-old brother of one of the original cases. On post-mortem, his heart showed almost identical appearances to those of his sister, thereby establishing the inherited basis of the disease.<sup>1</sup>

The family were described in detail in a subsequent paper, co-authored by Arthur Hollman, John Goodwin, and James Renwick, in which the entity was designated obstructive cardiomyopathy.<sup>16</sup> The same year, a second paper by the same group outlined the clinical profile of hypertrophic cardiomyopathy with left ventricular outflow tract obstruction, supplemented by results from the still emerging technique of cardiac catheterisation.<sup>17</sup> Co-investigator and cardiothoracic surgeon William Cleland also described successful alleviation of left ventricular outflow tract obstruction by septal myectomy under cardio-pulmonary bypass. The 42-year-old patient had a 4 year history of exertional chest pain and syncope and the procedure rendered him symptom-free for several years.<sup>4,17</sup>

In a classic example of the phenomenon of simultaneous discovery, termed "multiples" by science historians, groups around the world began to recognise and report the obstructive form of hypertrophic cardiomyopathy. Noteworthy were Bernard Bercu and co-workers in Missouri, who overturned the traditional tenet that ventricular hypertrophy is always a response to increased afterload, from aortic stenosis or systemic hypertension.<sup>4,18</sup> As in Brock's original account, the cases identified by Bercu et al were characterised by a concentric pattern of hypertrophy.<sup>18,19</sup> Bercu also drew attention to the familial preponderance of the condition,<sup>18</sup> an aspect that was further developed by Lawrence Brent and colleagues in Pittsburgh in their description of a family with muscular subaortic stenosis. The Pittsburgh group examined the pedigree and remarked on apparent Mendelian autosomal dominant inheritance.<sup>20</sup> Perhaps the largest family study came from J.A.P. Paré and colleagues in Montreal, who examined 77 members of a French-Canadian kindred covering 4 generations.<sup>21</sup> The adopted terminology was hereditary cardiovascular dysplasia; affected individuals showed features typical of hypertrophic cardiomyopathy; a high incidence of sudden death and cerebrovascular events was also apparent.<sup>21</sup> In Toronto, Douglas Wigle and co-workers underscored the occurrence of right as well as left ventricular outflow tract obstruction in a 10-case series.<sup>19</sup> Critically, Wigle determined on the basis of haemodynamic data that the increased muscle mass was associated with impaired diastolic filling secondary to reduced ventricular compliance. Diastolic dysfunction is now recognised to be one of the main functional consequences of hypertrophic cardiomyopathy. In concordance with Brent, Wigle favoured the term muscular subaortic stenosis.<sup>19</sup>

Meanwhile, at the National Institutes of Health (NIH) in Bethesda, Eugene Braunwald and Glenn Morrow coined the term idiopathic hypertrophic subaortic stenosis, which also gained widespread acceptance.<sup>22</sup> His interest sparked by a visit to William Cleland and Hugh Bentall in London, Morrow pioneered subaortic ventriculomyotomy, combined with limited resection of the hypertrophied muscular mass, to relieve left

ventricular outflow tract obstruction. The NIH experience with the technique in 25 patients was reported in 1968.<sup>23</sup> The frequent presence of mitral regurgitation on preoperative cineangiography was noted, as was the competence of the mitral valve on palpation at the conclusion of the operation. Resolution of mitral regurgitation was observed in 4 of 5 patients with this feature who underwent repeat post-procedure catheterisation. Of 23 surviving patients, followed for 1-8 years post-operatively, 15 remained asymptomatic and a further 6 had only mild residual exercise limitation.<sup>23</sup>

The existence of a variety of disease names, each one reflecting the perspective of a particular investigator, is considered characteristic of the second stage of the discovery process.<sup>2</sup> The Adelmans also emphasise that each perspective contains a fundamental conception that will be corroborated and assimilated into the final disease profile. The recognition of diastolic dysfunction, Mendelian autosomal dominant transmission, and different patterns of hypertrophy attest to this gradual unfolding of the clinical picture.<sup>19,20</sup> Stage III in the Adelmans' discovery process is defined by a general consensus on the key features of the disease, marred by a lack of comprehension of its aetiology.<sup>2</sup> Focusing on left ventricular outflow tract obstruction, the Adelmans point to the myriad theories of the 1960s regarding the underlying mechanism. Resolution (phase IV) came in 1966, when Fix et al in Stockholm and Dinsmore and colleagues in Boston identified movement of the anterior mitral valve leaflet towards the septum during systole on angiography.<sup>24,26</sup> Two years later, Pravin Shah and his co-workers confirmed systolic anterior movement (SAM) of the mitral leaflet as the cause of left ventricular outflow obstruction, using simultaneous recordings of the ECG, phonocardiogram, carotid artery pulse, and the then-emerging technique of reflected cardiac ultrasound.<sup>27</sup>

According to the Adelmans, the fourth phase in the discovery process entails assimilation of the clinical, pathological, and physiological features into a single coherent disease theory. Yet the Adelmans presented their case study of hypertrophic cardiomyopathy in 1977,<sup>2</sup> when the puzzle was but semi-complete, in spite of the emergence of a satisfactory explanation for left ventricular outflow tract obstruction. Contemporary data suggest that only 25% of patients with hypertrophic cardiomyopathy have significant resting left ventricular outflow tract obstruction, although the perception persists that obstruction is the defining feature of the disease, underscoring the profound and lasting impact of the studies from the late 1950s and 1960s.

In the ensuing decades, conceptions of hypertrophic cardiomyopathy continued to evolve, in line with the development of new technologies. The dominance of cardiac catheterisation as a diagnostic tool had naturally focused attention on the haemodynamic consequences

of the obstructive form of hypertrophic cardiomyopathy. The advent of M-mode echocardiography allowed in vivo measurements of left ventricular wall thickness and shed further light on the mechanism of obstruction, by demonstrating systolic anterior motion of the mitral valve leaflet and partial mid-systolic closure of the aortic valve. As M-mode was supplanted by 2-dimensional echocardiography, there was growing recognition of different forms of left ventricular hypertrophy, including concentric, asymmetric septal, distal/apical, midventricular, and isolated lateral forms.<sup>29-31</sup> Doppler techniques allowed non-invasive assessment of pressure gradients, mitral regurgitation, and diastolic function.

In 1995, Robert Levine, Arthur Weyman and colleagues reported that obstructive hypertrophic cardiomyopathy was associated with primary structural abnormalities of the mitral valve apparatus, the most important of which was anterior displacement of the papillary muscles. This predisposes to SAM of the anterior mitral valve leaflet in 3 ways: *a*) by reducing the posterior tension conferred by the papillary muscles on the mitral valve; *b*) by increasing the proximity of the leaflets to the left ventricular outflow stream; and *c*) by pulling the posterior leaflet upwards so that it meets the anterior leaflet near its midportion, thereby leaving a long portion of the distal leaflet unrestrained and susceptible to anterior forces. Incomplete coaptation of the leaflets also results in posteriorly directed mitral regurgitation. The nature of the haemodynamic force has been subject to debate, with 2 potential mechanisms in contention: the "pull" of Venturi effect versus the "push" of the flow drag effect. Using Doppler echocardiography, Mark Sherrid and colleagues demonstrated that SAM begins very early in systole, when the outflow tract velocity is normal. The relatively low velocity is unlikely to generate significant Venturi forces; conversely, there will be increased contact of the flowing blood with the valve, augmenting the drag effect.<sup>33</sup>

Paradoxically, inherited cardiovascular disease specialists appear now to have come full circle in their views on the importance of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. While the majority may not have a significant resting gradient, around two-thirds of symptomatic patients with hypertrophic cardiomyopathy have latent left ventricular outflow tract obstruction, which can be unmasked by exercise stress echocardiography.<sup>34</sup> Effective, evidence-based pharmacological therapy began with propranolol<sup>35</sup>; today, beta-blockers are still the mainstay of drug treatment for exertional outflow obstruction, while a multi-centre collaborative study has demonstrated the efficacy and safety of disopyramide in patients with significant resting gradients.<sup>36</sup> Percutaneous alcohol septal ablation is increasingly performed, but the septal myectomy procedure remains the gold standard for drug-refractory symptoms.<sup>37</sup>

Teare's original account went beyond septal hypertrophy, however, in also establishing hypertrophic cardiomyopathy as a cause of sudden death in young people.<sup>1</sup> In the early 1980s, Barry Maron and colleagues in the United States highlighted hypertrophic cardiomyopathy as the most common aetiology of sudden unexpected death in competitive athletes. Concurrently, in the UK, retrospective studies conducted by John Goodwin, Celia Oakley, William McKenna, and co-workers revealed a 2%-6% annual mortality rate in untreated patients with hypertrophic cardiomyopathy at a tertiary referral centre.<sup>39</sup> A family history of sudden death and the presence of non-sustained ventricular tachycardia on ambulatory ECG monitoring were among the first risk factors to be identified,<sup>39,40</sup> and remain pertinent to this day.<sup>41</sup> During this period, the implantable cardioverter defibrillator was still an experimental device, placed in the abdomen, and requiring thoracotomy for epicardial patch placement; recipients were confined to survivors of previous, usually multiple, cardiac arrests.<sup>42</sup> Lacking the luxury of a definitive solution for primary prevention of events, pharmacological treatment with amiodarone was employed; this appeared to have some efficacy in suppressing ventricular arrhythmia and a possible survival benefit in hypertrophic cardiomyopathy.<sup>43,44</sup> Since then, the advent and widespread availability of the modern implantable cardioverter defibrillator has provided clinicians with a highly effective if somewhat crude means of preventing sudden death. The early work on identification of prognostic indicators has been expanded over a 20-year period, culminating in a non-invasive risk prediction algorithm for hypertrophic cardiomyopathy, with a negative predictive value exceeding 95%,<sup>41</sup> reviewed by Maron and McKenna in the 2003 consensus statement on the disease.<sup>45</sup>

In the conclusion to their treatise on hypertrophic cardiomyopathy, the Adelmans recognised that further research on a different level was still needed. With remarkable prescience, they suggested in 1977 that the next key advancement might take place in the field of genetics.<sup>2</sup> Thirteen years later, and 32 years after Donald Teare's description of the disease, hypertrophic cardiomyopathy became the first inherited cardiovascular disorder to be successfully genotyped. In the Seidmans' laboratory in Boston, a disease-causing mutation was identified in the gene encoding cardiac beta-myosin heavy chain (*MYH7*), coincidentally in the same family that Paré et al had described back in 1961.<sup>21,46</sup> A distinct missense mutation in *MYH7* was subsequently isolated in the family originally reported by Hollman, Goodwin and Teare.<sup>47,48</sup> In the decade that followed, various other sarcomeric proteins were implicated in hypertrophic cardiomyopathy, including  $\alpha$ -tropomyosin, cardiac troponin T, troponin I, myosin binding protein-C, regulatory myosin light chain, essential myosin light

chain, cardiac actin, titin,  $\alpha$ -cardiac myosin heavy chain and troponin C.<sup>49</sup> This led to the concept of hypertrophic cardiomyopathy as a disease of the sarcomere, the contractile apparatus of the cell. Analysis of genotype-phenotype correlations further demonstrated that myocardial hypertrophy was not essential for diagnosis; certain mutations in troponin T, for example, may be associated with subtle or absent hypertrophy but a high incidence of sudden death.<sup>50,51</sup> Thus emerged the prevailing perspective of hypertrophic cardiomyopathy as an inherited heart muscle disorder caused by mutations in sarcomeric proteins, resulting in myocyte disarray, with or without fibrosis, myocardial hypertrophy, and small vessel disease (narrowing of intramural coronary arteries by medial thickening). The importance of recognising non-sarcomeric variants, termed phenocopies, has also been emphasised, not least because rational therapies may be available, such as enzyme replacement in Fabry's disease.

Nevertheless, the argument can be made that our understanding of hypertrophic cardiomyopathy has not yet reached the fourth stage of disease discovery process postulated by the Adelmans.<sup>2</sup> In spite of the insights provided by molecular genetic analysis, a coherent unifying mechanism for the pathogenesis of hypertrophic cardiomyopathy remains elusive. As is typical of stage III comprehension, theories abound, ranging from the contractile deficit hypothesis of Marian to the newer energy depletion premise of Ashrafian and Watkins.<sup>2,52,53</sup> Much of the incentive for these efforts is to identify novel therapeutic targets, ultimately leading to the Holy Grail of a cure for hypertrophic cardiomyopathy. In the 21st century, as we commemorate the iconic achievements of Donald Teare and others, it behoves us not only to recognise how far we have come, but also envision the long road we have still to travel.

## ACKNOWLEDGEMENTS

Srijita Sen-Chowdhry was supported by a Walport Clinical Lectureship. The authors would like to thank Shaughan Dickie for her assistance in researching this manuscript.

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