Valve disease continues to be an important cause of global disease load, with a high incidence in the developing world due to inflammation (mainly rheumatic disease) and an increasing number of patients in the developed world affected by "degenerative" valve disease due to increasing longevity coupled with a background incidence of rheumatic (often unrecognized) and infective endocarditis. This is reflected in the database of the American Society of Thoracic Surgeons and the UK Valve Registry, which have shown a progressive increase in the number and age of patients undergoing valve operations (Figures 1 and 2).

Valve replacement has markedly improved the natural history of the disease; however, residual subtle abnormalities of the heart or other organs can persist. At least some of these abnormalities are related to the inherent properties of the valve substitute and might conceivably be avoided or alleviated by a more restorative operation. Although repair is theoretically and intellectually more appealing, there is concern about its capacity to produce predictable, durable, superior results applicable to different types of valve disease compared with replacement. In addition, there have been continued improvements in the design and performance of valve substitutes. These potentially confounding factors can result in difficulties in choosing the optimal form of surgical treatments for specific patients with different forms of valve disease. A rational approach to this problem depends on thorough understanding of the complex sophisticated normal function and structure of each valve and the interaction of valves with each other as well as with other components of the heart, particularly the myocardium. This should be coupled with defining the nature and effect of different pathological processes and therapeutic maneuvers on specific functions and structures of the valve and the possible link to clinical progress as assessed by survival and quality of life. Recent progress in these areas has resulted in the accumulation of a considerable amount of knowledge relating to this subject.

In this article, we discuss some of these topics, with specific reference to evolution and application of different reparative procedures and the relation of structure to function, and we outline areas for future research.

From Structure to Function

Each cardiac valve performs several intricate, deceptively simple (Figure 3) functions, which are closely coordinated. These functions depend on a specific macrostructure and microstructure. Valve tissue is formed of a specific form of connective tissue framework: interstitial cells and matrix covered by endothelial cells. Although cardiac valve tissue is relatively avascular, it has been shown to be innervated by nerve fibers and endings that contain active sympathetic, parasympathetic, and peptidergic neurotransmitters. The interstitial cells have been shown to express smooth muscle α-actin and sarcomeric proteins specific to striated muscle that are thought to be, at least in part, responsible for the specific contractile properties of valve tissue. In addition, these cells express a variety of genes that determine their specific 3D structure (Figure 4), polarity, and contractile, secretory, and mitogenic responses to different physiological, pathological, or pharmacological stimuli. Interstitial cells communicate with each other through a system of cellular processes (Figure 4A) and specific gap junctions that are thought to play an important role in many of the functions specific to these cells. The extracellular matrix (ECM) is composed of a system of fibrils, hyaluronic acid, proteoglycans, and glycosaminoglycans. The ECM performs many essential functions, which include maintaining the spatial relationships of the cells, contributing to the physical properties of valve tissue, and most importantly, influencing the function of the cellular components of the valve through a 2-way communication system. The ECM is subject to dynamic remodeling by adjoining cells as well as membrane-bound and secreted proteases. The latter include matrix metalloproteinases and their tissue inhibitors (TIMPs). The pattern of expression of these enzymes is specific to each valve and can be altered during disease process.

Valve components appear to renew themselves continuously. In an experimental study in rats, protein replacement tagged with [3H]proline was significantly higher in the basal...
third of the leaflet than elsewhere, whereas glycosaminoglycan renewal labeled with [3H]glycosamine was higher in the areas of leaflet attachment to the aortic wall, suggesting a relationship between tissue renewal and local stress.26 The endothelial cells, particularly those on the ventricular aspect of the aortic valve, are subjected to very high and varied mechanical stresses. The specific characteristics that enable them to withstand and possibly respond to these stresses are not known; in addition, the rate of turnover of these cells has not been studied. With the exception of the pulmonary valve, all cardiac valves are located centrally within the heart and are closely linked by the fibrous skeleton of the heart27 (Figure 5). The proximity, structural continuity, design characteristics, and hemodynamic factors play an important role in providing essential “crosstalk” to achieve optimal single and collective function of the valves.28 This functional and structural integration of the 3 valves and the myocardium is the result of looping of the heart tube during development, an essential feature of vertebrate hearts that is thought to have evolved to support their dynamic circulation.29 Apart from helping to coordinate the function of the valves, looping and asymmetry30 provide a substrate for morphodynamic interaction between momentum and directional changes of the blood on the one hand and rhythmic contraction of the myocardium on the other.29

This integrated system of flow through the heart depends on a combination of elegant patterns of flow in and out of the valves that blend but never collide30 (Figure 6). These systems of flow could have relevance to the efficient functioning of the circulation and therefore should, wherever possible, be preserved after valve repair.

Morphogenesis of Heart Valves

Valve Development: Molecular and Cellular Insights

Determining the relationships between molecular, cellular, and morphological aspects of valve development is essential for understanding how they achieve their mature function. Such an understanding can also contribute to the evolution of new strategies for surgical treatment, including the rapidly advancing field of tissue engineering of valves.

There is now compelling evidence that the development of heart valves is the result of interaction between a tightly regulated genetic program and fluid mechanical stimuli acting through specific intracellular and intercellular processes.31 The genetic program involves a variety of regulatory molecules,32 including homeobox genes33 (Msx1, Mox1), basic helix loop helix (bHLH) factors, retinoic acid receptors, members of the transforming growth factor-β superfamily, the Wnt/β catalytic pathway,34 vascular endothelial growth factor, and endothelins, to mention but a few! These molecules are expressed in developing valve tissue at specific time points. In addition, transgenic mice lacking function of some molecules, such as endothelial constitutive nitric oxide synthase, endothelin, or nuclear factor of activated cells (cytosolic) (NFATc),35,36 develop abnormalities of the cardiac valve or ventricular outflow tract.

During development, valve cells originate from 3 main sources (Figure 7). The initial tissue (and the probable principal source of cells in both the fetal and adult valve) is
the overlying endocardium. Some of its cells undergo an epithelial-to-mesenchymal transformation, enabling them to migrate into the matrix. This process is regional and is initiated by factors secreted by the adjacent myocardium. Cells from 2 extracardiac sources can also be found in the developing valve leaflets: epicardial cells in the AV valves and neural crest cells in the outflow valve (Figure 7).

The dominant component of the postnatal valve is its ECM, which has asymmetrical distribution and composition in the different valves. This develops during the prenatal period and continues throughout life through interaction between cells, enzymes, and genetic and environmental factors, including hemodynamic forces. Research in this area is particularly relevant to valve repair operations and tissue engineering.

Aortic Valve and Left Ventricular Outflow

The aortic valve mechanism forms an integral part of the left ventricular outflow and aortic root, which together perform an essential function of unidirectional transmission of very large amounts of blood during a relatively short period of the cardiac cycle while maintaining laminar flow, optimal coronary circulation, myocardial function, and the least tissue damage during widely variable and frequently changing conditions. For the sake of convenience, the aortic outflow can be divided into the subvalvar region (or left ventricular outflow tract, LVOT) and the aortic root, which extends from the level of the crown-shaped annulus to the level of the sinotubular junction. The LVOT consists of a fibromuscular structure with the muscular and membranous septa forming the anterior wall and the subaortic curtain and anterior leaflet of the mitral valve forming the posterior wall. The right and left fibrous trigones join the anterior and posterior walls and act as hinge mechanisms, which play an important role in maintaining the dynamic behavior of the LVOT (Figure 8). The aortic root incorporates the valve mechanism and consists of the crown-shaped annulus, leaflets, commissures, subcommissural trigones, sinuses of Valsalva, and sinotubular junction. The component parts of the aortic root change in size and shape during the cardiac cycle. These changes and their relevance are currently the subject of intensive research (Figure 9). The instantaneous changes in aortic valve orifice have been shown to precede movement of blood in the ventricle and therefore could have implications important to ventricular function. Distensibility of the aortic root results in smooth closing and opening characteristics with transformation of the aortic orifice from the closed position to a triangle, then to a circle, without causing flexion deformity of cusp tissue. The shape of the aortic root plays an important role in maintaining systolic coronary flow, particularly during exercise. This depends on maintenance of laminar flow through the valve, coupled with vortices in the sinuses of Valsalva (Figure 3).
Mitral Valve Mechanism

The mitral valve forms the major component of the left ventricular inflow tract and therefore by necessity plays an important role in different aspects of left ventricular performance. The major portion of blood flow through the mitral valve occurs during the early part of diastole and depends primarily on passive forces, with a contribution from movement of the mitral annulus, active relaxation of the left ventricular myocardium, and possibly of the mitral annulus. This early flow not only is essential for maintaining low left atrial pressure, particularly during exercise, when tachycardia results in marked shortening of diastole, but also contributes to providing optimal stretch of the myocardium, which regulates the “force” of the next beat according to the Starling mechanism. To perform these important functions, the mitral orifice needs to be larger than the aortic outflow and more dynamic, with marked changes in the size and shape of the orifice during different parts of the cardiac cycle.46,47 It is of interest that enlargement of the mitral orifice starts before the end of systole and diminution in size starts during late diastole “almost in anticipation” of hemodynamic events46 (Figure 10). The mitral valve apparatus consists of the annulus, leaflets, chordae, and papillary muscles. The annulus changes its shape both in the horizontal plane and in the vertical plane, where it changes its shape from a saddle48 shape to a more flat structure (Figure 11). These changes (or lack thereof) may have implications to stress distribution on the cusps48 and valve function and therefore (at least in theory) can influence the result and durability of reparative procedures.

The structure of each component closely reflects the functional aspects, with the mitral annulus formed of an anterior, relatively rigid fibrous component extending between the 2 fibrous trigones and more “contractile” lateral and posterior components. The papillary muscles vary in configuration but are generally grouped into 2 heads with the chordae attached in a semicircular fashion, which mirrors their chordal attachment to the leaflets.49 The chordae can be classified into major fixing, marginal, and commissural according to their mode of insertion into the valve (Figure 12). The size, shape, orientation, and mode of insertion of the chordae reflect their function. The commissural chordae have a fan-like arrangement, with alternative branches attaching
the free border of the adjoining leaflet. In contrast, the major fixing chordae are relatively thick and have 3 sets of branches, the proximal or “strut” chordae attached to the ventricular aspect of the leaflet, and therefore determine the degree of curvature during systole and are thought to be implicated in the pathogenesis of mitral regurgitation associated with dilated ischemic or idiopathic cardiomyopathy. The marginal and lateral fixing chordae are attached to the free margin of the leaflet in a uniform manner and therefore prevent prolapse of any part of the free border. Understanding the function, orientation, and structure of the different chordae could be of importance in executing efficient valve repair. The leaflet, chordae, and papillary muscle contribute to the long-axis function of the left ventricle and should be preserved whenever possible.\textsuperscript{50} Development of chronic mitral regurgitation produces progressive left ventricular dysfunction,\textsuperscript{51–53} which includes abnormalities of the torsion dynamics.\textsuperscript{54}

Conversely, myocardial function can influence mitral valve function, with varying degrees of mitral regurgitation developing as a (direct) result of left ventricular dysfunction.\textsuperscript{55–57} Initially, this was thought to be secondary to papillary muscle dysfunction.\textsuperscript{58} More recent work suggests that the inotropic state of the myocardium has very little or no effect on mitral valve competence (Figure 13) and that the main cause of mitral regurgitation in heart failure is physical downward and outward displacement of the papillary muscles. This results in increasing the “tethering” forces on the mitral leaflets with diminution in the coapting forces.\textsuperscript{59} Because the mitral and aortic valves share the same orifice in the LV myocardium, there is strong interaction between these 2 valves\textsuperscript{59} (Figure 9).

**Tricuspid Valve**

Like the mitral valve, the tricuspid valve forms an integral part of the inflow tract to the right ventricle but is separated from the pulmonary artery by the right ventricular myocardium and infundibulum. The right ventricular shape resembles a flattened tube wrapped around the flask-shaped left ventricle. Although the tricuspid valve shares several of the

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**Figure 7.** Three known sources of mesenchymal cells found in valve precursor “cushion tissue” are shown in this diagram of a sagittally sectioned preseptation embryonic heart and transversely sectioned neural tube (not to scale). Some endocardial cells become mesenchymal (1), cranial neural crest cells migrate to pharyngeal arch reach and thence into outflow tract cushions (2), and subepicardial cells enter AV cushions through breaks in AV myocardium after migration from epicardial organ over outer surface of heart. For further details see text. AV indicates atrioventricular junction; OFT, outflow tract. Neural crest cells (stained blue) are readily detectable in late fetal semilunar valves (top panel) of a transgenic mouse engineered to allow neural crest cells to be identified. Very few are found in adult valve (middle panel), suggesting their subsequent death or a failure to divide. In contrast, populations of neural crest descendants remain significant in proximal great arteries (bottom panel). aAo, Aortic arch; Ao, Aortic valve in innominate artery; Ica, left carotid artery; Isca, left subclavian artery; rca, right carotid artery; rsca, (position of) right subclavian artery; PT, pulmonary trunk. Full photo origin details: Top panel, from Gittenberger-de Groot AC, Bartelings MM, Bogers AJJC, et al. Embryology of common arterial trunk. Prog Pediatr Cardiol. 2002;15:1–8, Figure 5d. Middle and bottom panels, from Reference 38, Figure 5b and 5a, respectively.

**Figure 8.** Structures surrounding left ventricular outflow tract and interactions between mitral and aortic valve orifices during systole with fibrous trigones acting as a hinge mechanism for movement of subaortic curtain. From Reference 28, Figure 2.
basic anatomic and functional characteristics of the mitral valve, it has a larger orifice and a more dynamic annulus attached at one point to the right fibrous trigone and is crossed by the conducting tissue. The tricuspid annulus has a complex 3D shape and does not conform to a flat ring. The mural leaflet is the largest in both the circumferential and radial directions, and the septal leaflet is the smallest. The chordal attachment and papillary muscle grouping of the tricuspid valve are not as constant as in the mitral valve, with several chordae supporting the septal leaflet being attached directly to the interventricular septum. This could have important implications to valve function, which can be influenced by the position of the interventricular septum. Banding of the pulmonary artery in patients with transposition of the great arteries and tricuspid regurgitation can result in a shift of the ventricular septum and improvement in tricuspid regurgitation.

**Mechanisms of Valve Dysfunction**

Regardless of the cause of acquired valve dysfunction, a number of common changes in the components of valve tissue which are occasionally produced by changes in surrounding tissues. These changes include deformation, tethering, tissue thickening and/or calcification, fusion, retraction, stretching, dilatation, or rupture. Understanding the cellular and molecular changes responsible for the late progress and the likelihood of recurrence is essential for optimal timing and choice of operation. In addition, such knowledge could provide novel therapeutic targets in the future.

In the aortic position, the evolution and progression of valve stenosis appears to be linked to inflammatory processes. This applies to rheumatic, congenitally bicuspid valves or stenosis of a previously normal valve in the elderly.\textsuperscript{60–62} In the latter conditions, the process is analogous to that occurring in atherosclerosis, with abnormal lipid profile and possibly hypertension playing an important role.\textsuperscript{62} Aortic valve calcification is thought to be a result of a combination of a passive dystrophic process in degenerating connective tissue and an active process with local expression of genes encoding such proteins as osteopontin, osteocalcin, and bone morphogenetic proteins. In the mitral position, acquired stenosis is almost exclusively secondary to rheumatic affection. Mitral annular dystrophic calcification and ossification in the elderly and some patients with the floppy valve syndrome spares the cusps and therefore has little functional effect. However, annular calcification needs to be carefully considered in planning and executing repair in patients with floppy-valve syndrome.\textsuperscript{63,64} The processes responsible for valve regurgitation include stretching, dilatation, or destruction of valve components because of intrinsic
changes or as a result of changes in surrounding tissue such as the myocardium or ascending aorta. The destruction is usually secondary to infective endocarditis or other inflammatory processes, whereas the stretching is caused by an imbalance between regenerative processes and matrix modulation by enzymes such as matrix metalloproteinases and their inhibitors, which could be influenced by hemodynamic and/or genetic factors. Recent experimental evidence in our laboratory suggests that humoral and/or pharmacological agents such as endothelin and 5-hydroxytryptamine (serotonin) may affect valve competence.

The recent development and application of noninvasive methods to characterize the structure and instantaneous movement of valve components coupled with genetic, molecular, computational simulation, and biochemical status should help to elucidate further the mechanisms of valve dysfunction. This knowledge could also provide novel targets for therapy in the future.

**Imaging Valve Function and Structure**

Recent and continued evolution of imaging heart valves has provided further insights into the structure, instantaneous movements, and detailed function of the valves and importantly, linking structure and function.

Modalities such as 2D echocardiography, MRI, electron beam tomography, and spiral computed tomography are used routinely for evaluating heart valve disease. The size of the different components of each valve, the site and extent of cusp coaptation, and the angle of closure can be followed and can, in the future, influence management in terms of both timing and choice of procedure. 3D echo and possibly MRI molecular imaging could provide further information in the future.

**Acknowledgments**

We thank Penny Thomas, DPhil, for her invaluable contributions to the section on morphogenesis and Dr Patricia Taylor, PhD, for supplying figures of interstitial cells.
Figure 13. Diagram showing mitral leaflet remodeling (thin arrows) caused by redistribution of chordal tethering (thick black arrows) and coapting forces (dotted arrows) during apical (A) and posterolateral (PL) displacement. Apical displacement of papillary muscles resulted in an apical shift of leaflet coaptation line. Posterolateral displacement of papillary muscles caused a posterior shift of leaflet coaptation line. Therefore, chordal coapting force component of anterior leaflet increased, generating a nonuniform regurgitant orifice area. N indicates normal. From Nielsen SL et al. J Am Coll Cardiol. 1999;33:843–853, Figure 7.

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Novel Approaches to Cardiac Valve Repair: From Structure to Function: Part I
Magdi H. Yacoub and Lawrence H. Cohn

Circulation. 2004;109:942-950
doi: 10.1161/01.CIR.0000115633.19829.5E
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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