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Mitral insufficiency : mechanisms of production : valvular pathology

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MITRAL INSUFFICIENCY:
MECHANISM OF PRODUCTION--VALVULAR PATHOLOGY

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I. INTRODUCTION AND HISTORICAL ASPECTS

"Our present concept of mitral insufficiency has evolved during the past fifty years. Its existence, as a clinical entity, was nearly denied early in the century and with this view the apical systolic murmur was relegated to an unimportant position. Following this, there was a gradual appreciation that both organic and functional mitral insufficiency were of clinical significance. This was based on long term observation of patients with acute rheumatic fever and rheumatic heart disease and a renewed interest in chronic valvular disease of all types. Studies of the systolic murmur and the development of phonocardiography helped to clarify the problem. Current concepts of mitral valvular disease(both stenosis and insufficiency) are based on new knowledge of the anatomy and physiology of this valve acquired through surgical procedures, a review of the pathology of the valve, and right and left heart catheterization. While as yet incomplete, they are quite different from those of the eta preceding mitral valve surgery only a decade ago"[39]

As mentioned above by Vander Veer, current concepts of mitral valve disease are much indebted to cardio-vascular surgery for their rapid evolution. Knowledge and recognition of the importance of mitral regurgatation has, to great extent, paralleled the

advances in this surgical field. For the past five years the mitral valve has offered untold opportunity for the study of its incompetent state just as this same valve did thirteen years ago when stenosis was first successfully relieved by surgical means.[18] With the development of techniques of extracorporeal circulation and the increasing experience with commissurotomy for mitral stenosis, it was realized that many of the earlier concepts of valvular pathology and mechanisms of production of mitral insufficiency were wrong.[18] This gave great stimulus for critical review of valvular anatomy, pathology and physilolgy; thus, the increasing oppctunity to study the normal and diseased valves in their functional state at operation was used to good advantage.[18, 36] Concomitant advances in the nonoperative fields of phonocardiography, right and left heart catheterization, angiocardiography, dye-dilution studies, etc., in addition to contributing heavily to advanced concepts of mitral insufficiency, are now especially important in preoperative evaluation of the nature and degree of the defect.[3,5,8,10,22,23,28,34,42,43]

Moot testimony as to the rapidity of evolution of current concepts of mitral regrugitation is offered by the relatively brief discussions found in many recent textbooks, some of which ignorantly continue to dwell on old concepts of minor disability, benign course,

and lack of surgical therapy.[1,6,15,19,35,40] Although an apical systolic murmur has long been recognized as perhaps the commonest of all valvular findings, only the most recent literature has disputed older concepts that mitral insufficiency is a relatively benign lesion and as such is rarely the cause of untoward clinical symptoms leading to death.[18,29] It is now recognized that insufficiency of the mitral valve in undoubtedly a more insidious lesion than stenosis but that in time it creates even more serious effects on the myocardium of the left ventricle and atrium than does its stenotic counterpart.[18] "For the first time incompetence is being seen in its true perspective."[39]

(Citations in the appended bibliography best reviewing detailed historical development of concepts of mitral regurgitation include: Vander Veer[39] White,[40,41] Glover and Davila,[18] and Brigden and Leatham.[3])

II THE NORMAL MITRAL VALVE

Brief review of the normal mitral valve is essential for full understandin of the disaese mechanisms considered later. The following quotation excerpts from Brock give a concise review of itral valve anatomy and function with special emphasis on "critical areas of tendon insertion," important in his discussions of valvular closure and disease mechanisms.

"The normal mitral valve consists of the atrio-ventricular fibrous ring to which the cusps gain their attachments, of the two cusps, and of the papillary muscles with their chordae tendineae. The two cusps are anteriomedial and posterolateral, being so arranged that the axis of the valve orifice is directed obliquely forwards from right ot left" (Fig. 1)

Fig. 1: The Normal Valve Relationships--Superior Asect.

"The anteromedial or aortic cusp is much the larger and the more important in that during ventricular systole

it receives a great part of the stream of emergent blood which it prevents being driven back into the left atrium and helps to direct into the aortic outlet".

"The posterolateral cusp fulfills a secondary and supporting part in the closing of the mitral orifice in ventricular systole."

"The papillary muscles are typically two in number and lie opposite the intervals between the valve cusps; they arise from the ventricular wall at about the junction of the apical and middle thirds, one being anterolateral and one posteromedial. Both muscles are situated in the lower inflow portion of the left ventricle; the anterolateral one ariwing from the concavity of the anterolateral wall of the ventricle and the postero-medial from the junction of the septal and posterior surfaces. Each muscle... may be split to a greater or lesser degree..."[4]

"The chordae tendineae pass from each papillary muscle to gain attachment to both valve cusps in such a way that the anterolateral muscle and its tendons control the anterolateral half of the valve, and the paoteromedial muscle and its tendons control the corresponding posteromedial half (Fig.2) The chordae tendineae are of three orders according to Quain (1929).[33]

"I) Those which are inserted of the free edge of the cusps. They are numerous delicate threads which

arise from the other cords near the cusp margin, and often form a fine network before they are attached to it"[4]

"2) Those which are inserted at intervals on the ventricular surface of the cusp near its free edge, which they pass over to the attached border. They are distinctly thicker than the chordae of group 1, and those attached to any one cusp are derived from two different papillary muscles or from one papillary muscle and the wall of the ventricle."

"3) The short broad fibers that stretch across the perivalvular groove from the ventricular wall to the undersurface of the cusp near its base and run along the cusp a short distance towards its free margin."

For practical purposes the arrangement of the chordae tendineae may be simplified to two primary attachments on each cusp about two cm. apart; Brock terms these sites "the critical areas of tendon insertion" (Fig.2)

"These areas...are seen to be formed by those tendons that arise from the very summit of the papillary muscles and gain the most direct attachment to the valve cusps. These tendons are often slightly thicker and stronger, and clearly must exercise the most powerful selective action on the cusps since they are in the line of the direct pull of the papillary muscles. The more obliquely placed tendons which gain insertion on each side are of a secondary supporting nature."[4]

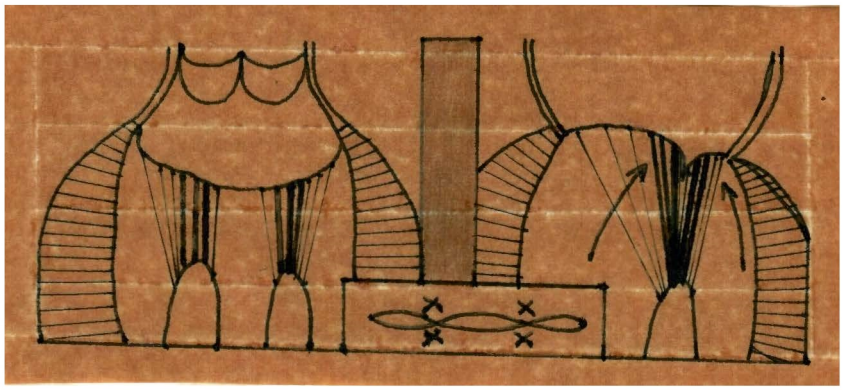

Figure 2.

"Diagram to show the probable mode of closure of the mitral cusps. The thicker chordae tendineae are those in the direct line of pull from the papillary muscles to the cusp. The small inset indicates the critical areas of tendon insertion thus formed; in these areas the cusps are held most tightly together."4

III CLOSURE OF THE NORMAL MITRAL VALVE

Differences of opinion still exist as to the exact mode of mitral valve closure. The cusps, chordae tendineae and papillary muscles are all important in this function, as is the ring itself, which is reduced in circumference during systole" [39] Since the mechanism described by Brock seems to fit best with the overall considerations of valvular anatomy, physiology, pathology, and physiopathology plus observations at surgery, it will be presented first.

" It is almost certain that the two cusps come together along their opposing surfaces, being driven into this position by the rise in pressure during ventricular systole." (Fig.2) There is considerable overlap of cusps possible in the normal valve. "There is little doubt that the aortic cusp is the main factor in effective closure of the orifice and the posteromedial cusp occupies a subsidiary or adjuvant function in sealing a narrow and probably variable crescent of the orifice."

"A possible alternative mechanism of closure is that the orifice is closed entirely by the anteromedial or aortic cusp forcing the much smaller posterolateral cusp against the posterior wall of the ventricle. It is doubtful if this is the usual mechanism, but it may well happen sometimes; it is unlikely to occur if

the A-V ring is at all dilated. In systole the inflow portion of the left ventricle is tightly contracted so that its cavity is almost completely obliterated, but sufficient space remains postero-inferiorly for the hydrostatic pressure to reach the ventricular aspect of the posterolateral cusp and its "free" area must be small. When the finger in introduced into the left atrium during an operation for mitral stenosis, the anteromedial cusp is usually very easily felt billowing upwards into the atrium like a sail filled with the wind; it is much more difficult to feel the postero-lateral cusp, and, indeed, its presence has often rather to be assumed by judging the distance that lies between the actual mitral orifice and the posterior part of the A-V ring."

"According or Quain[33] the distance between the apex and the base of the left ventricle does not shorten during contraction of the ventricle; the atrioventricular region moves upwards and backwards, but the length of the cavity remains constant. This makes it easier to understand how the comparitively small contraction of the papillary muscles is able to ensure efficient closure of the cusps being blown open into the atrium. The apposition of the cusp surfaces ensures their water-tight closing, but the pressure-resisting mechanism

comes from the musculo-tendinous support and its neuro-muscular co-ordination with ventricular systole. The mode of insertion of the tendons from one papillary muscle to each of the opposing cusps increases the efficiency of the mechanical closure of the valve." The fundamental importance of this mechanism is emphasiz ed by the severe and often fatal regurgitation which occurs abter damage to this mechanism by surgery or infarction, etc.; simple mechanical apposition of the cusps is not enough.[4]

"During ventricular diastole the papillary muscles and the tendons are lax and the cusps float open before the stream of blood from the atrium. During ventricular systole the valve cusps are flung tight together and the papillary muscles and tendons become taut and straight; the maximum, the most powerfully supported, closure must occur in relation to the critical areas of tendon insertion already described. At the height of systole the tendons passing from the summit of each papillary muscle direct to these two critical areas on the valve cusps must be tense and aprallel and very close to one another (Fig. 2); in contrast with during diastole... they are lax and directed outwards toward the wide open margins of the orifice. At these two critical areas the cusps must be held together very tightly indeed; The significance of this will become apparent later

when we consider the state of the diseased valve."[4]

Harken[18] indicates that closure is accomplished by 1) reduction in annulus size (with ventricular systole); 2) relaxation of leaflet edges as the chordae tendineae sre relaxed in systole; and 3) further securing of leaflet margin closure by the twisting motion of the ventricle and torsion of the chordae tendineae. This agrees in part with the ideas of Lutenbacher[27] who describes closure as a bunching up of valve cusps, chordae tendineae, and papillary muscles in such a way that closure of the orifice is aided and secured by an interlocking of these structures. Both of the mechanisms by Harken and Lutenbacher are, of course, at variance with Brock's theory presented above; they seem to ignore the observations at operation by Brock and others that the leaflets billow into the atrium and do not feel bunched up. Also Harken's description of lax chordae tendineae and leaflet edges does not seem plausible, considering the severe regurgitation caused by their rupture.[4,30] Torsion of the valve mechanism would have to be fairly marked to cause interlocking of any significance. Narrowing of the valvular orifice at the time of ventricular systole is mentioned by both Harken[18] and Brock.[4]

IV ETIOLOGY OF MITRAL INSUFFICIENCY

Mitral insufficiency may be grouped into 1) organic and 2) relative or functional etiologies. Organic insufficiency can be due to: a) rheumatic valvulitis: b) other less common causes of acquired insufficiency; and c) congenital defects. [15]

Many of the basic defects in the valvular mechanisms of insufficiency are common to more than one of the above etiologies. Moreover, more than one of the above etiologies may be responsible in any one given case, especially when organic versus functional groups are conserned.

Rheumatic valvulitis is responsible for most cases of mitral valvular disease, stenosis or regurgitation. Most authors emphasize that stenosis is usually combined with regurgitation and vice-versa; the predominate physiological defect is dependent upon the size of the valvular orifice.

Pathology and mechanisms of regurgitation in the less common nonrheumatic etiologies are often basicly similar to those of rheumatic origin. A major portion of the discussion of spedific pathophysilolgical defects will be made mnder the category of rheumatic valvulitis; production of similar defective mechanisms by other etiologies will be included in the discussion of that specific mechanism.

Other less common causes of acquired organic mitral insufficiency include: 1) traumatic rupture of a cusp or of the chordae tendineae; 2) spontaneous chordae tendineae repture; 3) repture of a papillary muscle secondary to bacterial endocarditis, or coronary occlusion; 4) bacterial endocarditis, per se; and "pure" mitral regurgitation. Study of the pathophysiology produced by these more or less "isolated" defects is of help in the full comprehension of the multiple mechanisms often responsible in the more common regurgitation of rheumatic etiology. Most of the traumatic -etioligies are secondary to commissurotomy or other heart surgery. The so-called "pure" organic mitral regurgitation as discussed by Brigden and Leatham[3] is of uncertain etiology; a marked male sex dominance, absent history of rheumatic fever, and absent stenosis are the outstanding characteristics.

Severe mitral insufficiency in children under five years old without a history of rheumatic fever is most often caused by congenital mitral valve disease. In contrast of older views, [1,19] recent literature indicates that incidence of congenital mitral insufficiency is relatively common compared to congenital mitral stenosis and other congenital heart disease, especially when associated with other cardiac malformations.[13,15,17] Incompetence may be due to ;

1) anomalous insertion of chordae tendineae; 2) shortened chordae tendineae secondary to endocardial sclerosis; 3) cleft leaflet; or 4) a maldeveloped valve associated with ventricular septal defect or persistant common atrio-ventricular canal.[13,15,7,37,38]

Relative or functional (nonorganic)mitral insufficiency often occurs as a result of left ventricular dilitation secondary to hypertensive, coronary, or aortic valvular disease, etc., uaually in association with left ventricular failure. "Imperfect valvular closure under such circumstances is due to dilitation of the mitral ring and to retraction of the cusps by chordae and papillary muscles as the ventricular chamber elongates."[15]

V. MECHANISM OF PRODUCTION--VALVULAR PATHOLOGY

Brock's opinions[4] of mitral regurgitation are based on observation of valve function at operation as well as careful studies of the pathologic changes of diseased valves, with and without operation. His ideas on normal mitral valve anatomy and closure mechanism have been reviewed above. "The valve mechanism extends over a distance of some 5 cm., and a lesion may affect all parts of it or one part more severely than another. A lesion at any level can seriously interfere with the mechanism, and it is not always the actual valve cusps that are most seriously affected." He stresses many facts relative to both mitral insufficiency and stenosis. He emphasizes that true mitral insufficiency is usually caused by the most severe grades of damage to the valve; the old view that insufficiency is a result of mild rheumatic valvulitis and stenosis from a more severe attack is an "erroneous oversimplification." Fusion of the valve cusps at the two opposing "critical areas of tendon insertion" (Fig. 2) is the fundamental occurrence in the production of mitral stenosis and is due to the increased pressure at these points, resulting from normal valve function (see above). The portions of opposing leaflets outside the critical areas on tendon insertion are then essential-

ly functionless and secondary adherence occurs(Fig. 2). The mild valvulitis required for this adherence is far less in degree than that required to distort the margins sufficiently to cause leakage; normal excess in overlap requires great margin rigidity and damage before insufficiency results, and it is still mild if this is its only mechanism. Significant regurgitation requires much more severe damage to the valve, frequently involving multiple mechanisms.

Brock[4] lists six fundamental mechanisms causing valvular incompetence; one, or more frequently, several, may co-exist, in varying grades of importance.

1) "A hole or defect in a valve cusp." This may be congenital or caused by malignant endocarditis or surgical trauma, etc., but is not a feature of rheumatic valvulitis.

2) "Rigidity of the margins of the valve orifice preventing its closure." As previously mentioned this seldom causes more than mild regurgitation through a stenotic orifice; valvulotomy often corrects the insufficiency at the same time.

3) "Rupture of the musculo-tendinous mechanism so that a cusp is unsupported in ventricular systole." This rare mechanism, secondary to infarction or surgery causes severe regurgitation emphasizing the importance of this mechanism.

4) "Shortening of one or both cusps so that they cannot meet and overlap." Severe damage to the whole substance of the cusp is needed. Relative shortening is caused by mechanisms 5) and 6).

5) "Shortening of the musculo-tendinous mechanism so that the valve cusps cannot rise and meet." This is usually due to valve adherence and scarring with contracture secondary to rheumatic valvulitis. Relative shortening of the musculo-tendinous control as a result of ventricular dilitation and increased ring diameter are added factors.

6) "Extreme dilitation of the atrioventricular ring leading to secondary relative shortening of the cusps." This plus ventricular dilitation both act to cause relative shortening of the musculo-tendinous control.

Three degrees of incompetence at operation are described by Brock:[4] 1) A small regurgitant stream from a grossly stenosed orifice; 2) a moderately powerful regurgitant stream from a narrowed but not grossly stenosed orifice; and 3) a powerful regurgitant stream with an orifice equal to or greater than the aortic outlet. Type 1 is easily corrected when stenosis is relieved and is minor in importance. Type 2 is more commonly seen and represents the most severe grades of rheumatic valvulitis. The total valve mechanism is

involved. The larger orifice results from the severe shortening and contraction of the cusps in all directions. Type 3 is associated with valve ring dilitation: this is prevented in type 2 by the dense fibrosis thus avoiding extreme imcompetence.

Harken[18] describes an upward herniation of the valve complex as "one of the many features of 'self aggravation'" of mitral insufficiency. The regurgitant jet dilates the auricle, displacing the annulus over the ventricular rim by traction. The effective component of leaflets posteriorly is reduced, increasing local incompetence as the valve complex is drawn over the ventricular rim. This local increase in regurgitation further aggravates herniation and relative shortening of leaflets. "It also explains the greater insufficiency posteriorly and posteromedially. As the valve complex moves upward, the chordae tendineae are drawn taut and interfere with leaflet closure. Similarly, compensatory dilatation of the ventricle not only enlarges the annulus but increases the tension on the chordae tendineae: both increase incompetence."

Harken complains that "the usual illustration of the mitral valve surface does not represent the upward herniation of the valve complex posteriorly and it does not indicate the leaflet limitation by chordae tendineae drawn taut by the upward migration of the leaflet complex and papillary muscles displaced down-

ward by ventricular dilatation." He believes that in normal valve closure the leaflet edges and chordae tendineae are relaxed in systole (see normal closure discussion) rather than the more widely accepted theory of mild tensing of chordae tendineae, acting as guy wires and thus preventing leaflet displacement by ventricular systolic pressure. (Brock[4]) If the theory of valve complex herniation is accepted, the regurgitation would seem to be due to relative deficiency of leflet substance--marked tension on chordae tendineae and leaflets resulting in a distorion of normal leaflet--chordae tendineae relationships.

Harken[18] recognizes five general morphologic patterns of mitral insufficiency:

Type I, absolute deficiency of substance due to scarred and contracted leaflets.

Type II, relative deficiency of substance due to annulus dilitation secondary to ventricular dilitation. This follows and is combined with Type I.

Type III, has predominate stenotic orifices facing the outflow tract with insufficiency as it "scoops up blood". (sometimes correctable by repair of stenosis).

Type IV, poor coaptation due to calcific leaflets, often associated with Type I.

Type V, is a common form of combined stenosis and insufficiency of varying degree of each with a stenotic anterior bridge (often calcified and a noncalified

incompetent area posteromedially.

An infinite varity of combinations of these types exist.

Glover and Davila[7,16] have given concentrated study to the problem of mitral insufficiency since 1952; they emphasize three basic pathologic changes resulting in insufficiency, namely: 1) absolute loss of valve tissue; 2) contraction and foreshortening of the chordae tendineae; and 3) dilitation of the mitral annulus. A few minor variations from the basic three features are occasionally found, especially with the far less common nonrheumatic etiologies , but these features were ample to cover most cases completely. In instances where authors present larger lists of basic mechanisms, usually all of the subdivisions can fit into these broader gourps.

Absolute loss of valve tissue is just about always due to rheumatic valvulitis, with congenital defects and malignant endocarditis being rare possibilities. The mural leaflet is usually affected most in the rheumatic forms.

Contracted and foreshortened chordae tendineae can cause considerable imcompetence with minimal leaflet damage but marked rheumatic leaflet dama e is most commonly present also, both factors resulting in an "absolute loss of valvular occluding elements." Since rupture of the papillary muscle or chordae tendineae results in the same basic effect of musculo-tendinous

dysfunction, any of the specific etiologies (as listed earlier) dealing with this mechanism would come under this feature.

Dilitation of the mitral ring is almost routinely present in the estimate of these two authors; it is often considered to be a result of the first two entities but may appear at the same time. This factor is especially important because dilitation of the left ventricle as a compensating mechanism for its increased output causes further valve ring dilitation and increased relative or functional insufficiency resulting in a further work load. Thus the ventricle wears out from overwork plus an ever increasing load.

Bodeman[35] makes sharp distinction between valvular insufficiency, due to deformity of the cusps, and incompetency, meaning leakage due to normal cusps not completely closing the orifice they guard. He has long been aware of the mechanism of mitral incompetence, his description and diagram (Fig.3) being almost classical in that regard. "Incompetency of the atrioventricular valves is related to ventricular dilitation, and is probably due principally to downward displacement of the sites of origin of the papillary muscles, with the result that perfect approximation of the cusps is prevented by the now relatively short chordae tendineae."

severe regurgitant disease. Levine and Harvy[22] emphasize that the resultant "functional" or "relative" murmur is by no means indicative of a benign disease.

Most of the other improtant reviews in this field tend to agree with one or a combination of views presented above. Gould[17] describes three basic types of mitral regurgitation other than postraumatic. 1) congenital deformity; 2) dilitation of the valve rihg; 3) and shortening or retraction of the mitral leaflets. Nichols[32] lists the three pathological entities of 1) retracted leaflets, 2) dilated mitral annulus, and 3) shortened chordae tendineae as responsible for insufficiency in the majority of cases. He also lists the infrequent entities of congential perforation on one or both leaflets, congenital cleft leaflets, and detachment of chordae tendineae; all of these major and minor entities fit into the three broader groups of Grover and Davila[7,16] given above. Lillehei[26] recognizes two major groups which are the same as those of Glover and Davila[7,16] if, as they suggested as an alternate possibility, the first two groups are combined to "absolute loss of valvular elements." White[40] stresses consideration of "functional" insufficiency as did Sodeman above, but he emphasizes rather than minimizes its importance. "Functional mitral insufficiency due to left ventricular

dilitation should not be regarded as a trivial condition." It is possible that the displacement downward of the papillary muscles as the result of the ventricular dilitation is a moreimportant factor in causing the mitral regurgitation than is dilitation of the A-V ostium, that is, of the valve ring. The chordae tendineae muscles moved away from the base of the heart their insertions on the valve cusps are likewise displaced downsard. This results in an inability of the mitral cusps to close tightly no matter how tautly the chordae may stretch or how normal or elastic the cusps may be; regrugitation of greater or lesser degree follows. Occasionally, in fact frequently, factors due to both left ventricular dilitation and to deformities of valve cusps and cordae tendineae combine to cause mitral regurgitation."

The valvular pathology in congenital heart disease as a cause of mitral insufficiency is produced by various processes of maldevelopment-- usually a failure of fusion--of the defective valve part. It is sometimes associated with endocardial sclerosis, etc. Mechanisms of product on of insufficiency by the various defects found(see etiology) are the same as when that valve part is affected by acquired disease.

VI SUMMARY AND CONCLUSIONS

Review of historical aspects of mitral regurgitation shows that most of out current concepts have been developed during the last decade. Cardiovascular surgery has been the major stimulus for investigation. It is now realized that although regurgitation may be of more insidious onset it often results in more severe disability and more rapid demise than with stenosis.

Brock[4] has shown that the entire valve mechanism including cusps, chordae tendineae, and papillary muscles must be considered for full understanding of all mechanisms of regrugitation. The importance of the musculo-tindinous mechanism and the "critical areas of tendon insertion" on the cusps is widely accepted as necessary for normal valve closure.

Etiology of regurgitation is primarily valvular damage of rheumatic heart disease. Other forms are discussed; congenital forms are more common than realized previously.

Mechanisms of production discussed by most recent authors seem to fall into the 3 basic groups of Grover and Davila: 1) absolute loss of valve tissue; 2) contraction and foreshortening of the chordae tendineae; and 3) dilitation of the mitral annulus. The first 2 groups are "absolute loss of valvular occluding elements"

and the last 2 one relative loss of valve tissue. The morphologic patterns described by various authors are listed and discussed. The importance of "functional" insufficiency of left ventricular dilitation with downward displacements of the musculo-tendenous system and cusps is emphasized by White and deserves wide recognition as an important basic mechanism.

VII BIBLIOGRAPHY

1. Anderson, W. A. D. and others, Pathology, 3rd ed., St. Louis, C. V. Mosby Co., Chap. 19(p. 457).

2. Bakst, A. A. and others, The Surgical Correction of Mitral Insufficiency by Use of a Pericardial Valve Graft, J. Thoracic and Cardiovasc. Surg. 35: 492, 1958.

3. Brigden, Wallace and Leatham, Aubrey, Mitral Incompetence, Brit. Heart J. 15:55, 1953.

4. Brock, R. C., The Surgical and Pathological Anatomy of the Mitral Valve, Brit. Heart J. 14:489, 1952

5. Carlier, Jean and Lejeune-Ledant, G. N., Pulmonary Artery Wedge Pressure in Experimental Mitral In-sufficiency, J. Thoracic and Cardiovasc. Surg. 38:2, 1959.

6. Cecil, R. L. and Loeb, R. F., ed., A Textbook of Med., 10th ed., Philadelphia, Saunders, 1959, pp. 1250-1251.

7. Davila, J. C. and others, A Method for the Surgical Correction of Mitral Insufficiency: Prelim. Con-siderations: Surg., Gyn., and Obstetrics Vol. 98; No. 4:407, (April) 1954

8. _____, Hemodynamics of Mitral Insufficiency; Observations from Clinical and Experimental Surgery, Am. J. of Cardiology 2: 135, 1958.

9. _____,and Glover, R. P., Circumferential Suture of the Mitral Valve for the Correction of Regurgitation, Am. J. of Cardiology 2: 267, 1958.

10. _____, The Clinical and Physiologic Criteria for Surgical Correction of Mitral Insufficiency, J. Thoracic and Cardiovasc. Surg. 35: 206, 1958.

11. _____, Normal and Pathologic Mechanics of Cardiac Valves; With Consideration Toward the Development of prosthetics (Abstract), Circulation, Vol. XXII; No. 4; Part Two: 738, 1960.

12. _____, Long Term Results for Mitral Insufficiency (Abstract), Circulation, Vol. XXII; No.4; Part two: 738, 1960.

13. Effler, D. B., Surgical Treatment of Mitral Insufficiency: Open Approach with Elective Cardiac Arrest, Am. J. of Cardiology 2: 276, 1958.

14. Ellis L. B. and others, Selection of Patients for Mitral and Aortic Valvuloplasty, Circulation, Vol. XV; No. 6: 924, 1957.

15. Friedberg, C. K., Diseases of the Heart, 2nd ed., Saunders, Philadelphia, 1956, Chap 26.

16. Glover, R. P. and Davila, J. C., The Treatment of Mitral Insufficiency by the Purse-String Technique, J. Thoracic and Cardivovasc. Surg. 33: 75, 1957.

17. Gould, S. E., Pathology of the Heart, 2nd ed., Springfield, Ill., C. C. Thomas, 1960, 390, 670,1030.

18. Harken, D. E., Mitral Regurgitation: A Group of Surgical Problems, Am. J. of Cardiology 2: 263, 1958.

19. Harrison, T. R., ed. and others, Principles of Internal Medicine, 3rd ed., New York, Blakiston, 1958, Chap. 224.

20. Kay, E. B. and others, Surgical Treatment of Mitral Insufficiency: Direct Vision Correction with Use of Mechanical Pump Oxygenator and Extracopporeal Perfusion, Am. J. of Cardiology 2: 281, 1958.

21. Kernan, M. C. and others, A Prosthesis to replace the Mitral Valve, J. Thoracic and Cardiovasc. Surg. 33: 398, 1957.

22. Levine, S. A. and Harvey, W. P., Clinical Ascultation of the Heart, 2nd ed., Philadelphia, W. B. Saunders Co., 1959, p, 225.

Levinson, D. C. and others, Evidence for Retrograde Transpulmonary Propogation of the V (or Regurgitant) Wave in Mitral Insufficiency, Am. J. of Cardiology 2: 159, 1958.

Levowitz, B. S. and others, Total Prosthetic Replacement of the Mitral Valve--An Experimental Study (Abstract), Circualtion, Vol. XXII; No. 4; Part Two: 779, 1960.

Lillehei, C. W. and others, The Surgical Treatment of Stenotic or Regurgitant Lesions of the Mitral and Aortic Valves by Direct Vision Utilizing a Pump-Oxygenator, J. Thoracic and Cardiovasc. Surg. 35: 154, 1958.

26. _____, Surgical Treatment of Aortic and Mitral Valve Lesions Utilizing Prostheses (Abstract), Circulation, Vol. XXII; No. 4; Part Two: 791, 1960.

27. Lutembacher, R. (1950) Le Rètrecessement Mitral, Paris. (cited by;) Brock[4].

28. Marshall, H. W. and others, Hemodynamic Methods for Differentiation of Mitral Stenosis and Regurgitation, Am. J. of Cardiology 2: 24, 1958.

29. Maurer, E. R. and Mendez, F. L., Remedial Lesions of the Mitral and Aortic Valves, Am. J. of Cardiology 2:292, 1958.

30. McGoon, D. C., Repair of Mitral Insufficiency due to Ruptured Chordae Tendineae, J. Thoracic and Cardiovasc. Surg. 39: 357, 1960.

31. Nichols, H. T., Mitral Insufficiancy: Treatment by Polar Cross-Fusion of the Mitral Annulus Fibrosis, J. Thoracic and Cardiovasc. Surg. 33: 102, 1957.

32. _____, Surgical Treatment of Mitral Regurgitation Utilizing Extracorporeal Circulation (Abstract) Circulation, Vol. XXII; No. 4; Part two: 793, 1960.

33. Quain's Anatomy, (1929). 11th ed. Vol IV, The Heart (cited by) Brock.[4]

34. Ross, John and others, Clinical and Hemodynamic Observations in Pure Mitral Insufficiency, Am. J. of Cardiology 2: 11, 1958.

35. Sodeman, W. A., ed., Pathologic Physiology: Mechanisms of Disease, 2nd ed., Philadelphia, W. B. Saunders, 1956, p 410.

36. Starkey, G. W. B., Surgical Experiencesin the Treatment of Congenital Mitral Stenosis and Mitral Regurgitation, J. Thoracic and Cardiovasc. Surg. 38: 336, 1959.

37. Starr, Albert, The Mechanism and Prevention of Air Embolism During Correction of Congenital Cliet Mitral Valve, J. Thoracic and Cardiovasc. Surg. 39: 808, 1960.

38. Talner, N. S. and others, Congenital Mitral Insufficiency, Circulation, Vol. XXIII,: No. 3: 339, (March) 1961.

39. Vander Veer, J. B., Mitral Insufficiency: Historical and Clinical Aspects, Am. J. of Cardiology 2: 5, 1958.

40. White, P. D., Heart Disease, 4th ed., New York MacMillan, 1951, pp667-683.

41. _____, The Evolution of our Knowledge about the Heart and Its Diseases since 1928, Circulation, Vol XV; No. 6: 915, 1957.

42. Wiggers, C. J. and Feil, Harold, The Cardio-dynamics of Mitral Insufficiency, Jeart 9: 149, L922.

43. Wilder, R. J. and others, Roentgen Contrast Diagnosis of Experimental Mitral and Aortic Insufficiency in Dogs by Transventricular Injection and Retrograde Catheterization, J. Thoracic and Cardiovase. Surg. 33: 147, 1957.