THE MITRAL VALVE

- AN EXPERIMENTAL STUDY WITH SPECIAL REFERENCE TO PROBLEMS IN THE DESIGN AND TESTING OF A MOBILE PROSTHESIS FOR THE SURGICAL CORRECTION OF MITRAL INSUFFICIENCY

A THESIS SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

BY

MALCOLM BETT McKENZIE

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF SURGERY

NOVEMBER 1960

INDEX

Functional Mitral Insufficiency.

1V. The Haemo-dynamic and Secondary Pathological Effects of Mitral Insufficiency.

THE PROBLEM

A RATIONAL APPROACH TO THE PROBLEM

MATERIALS

1. Tissue Grafts.

11. Artificial Materials

EXPERIMENTAL METHODS AND RESULTS

A. Method of Fabricating Silastic Valves.

B. Method of Fabricating Latex-rubber Valves and the Experimental Value of such Valves.

C. Method of Testing and Studying Valve Action in Vitro - The Pulse-Duplicator.

  1. Apparatus.
  2. Preparation of the Heart.
  3. Assembling the Pulse-Duplicator,
  4. Operating the Pulse-Duplicator.

D. Method of Testing Durability of Prosthetic Valves.

E. Method of Insertion of Prostheite Valves in Experimental Animals.

  1. The problem of Systemic Air-embolism during Open Left atriotomy
  2. Elective Ventricular Fibrillation for the Prevention of Systemic Air-embolism during Open Left-atriotomy.

INTRODUCTION

"The road to the heart is only 2-3 cms. in a direct line, but it has taken surgery nearly 2400 years to travel it ...... and it took surgery 98 years to pass from the pericardium to the epicardium, across a space that is such only potentially". Sherman[1] in 1902, succinctly summed up the history of cardiac surgery at that time with these words.

Since the beginning of the 20th century progress in cardiac surgery has been more rapid, but never before in the history of medicine has any generation witnessed such rapid advances in the treatment of disease as have occured in this field during the last decade. Prior to 1948, the treatment of heart disease was essentially medical, of necessity confined to the relief of symptoms as they arose and could not affect the basic cause, namely an anatomical abnormality. Bailey[2] in June, and Brock[3] in September of 1948, performed their now historical operations of mitral valvotomy for mitral stenosis which completely altered the prognosis of this previously incurable disease, and which marked the commencement of the modern era of direct attack on the underlying anatomical abnormality responsible for the production of symptoms of cardiac disease.

The progress during the present century has been in no small measure due to an improvement in those techniques which have facilitated all surgery, namely, improvements in anaesthesia, the control of haemorrhage and sepsis, and a better understanding of the physiology of shock and its management. It had long been recognised however, that progress in cardiac surgery was greatly dependent on a method of maintaining the metabolic requirements of the body tissues while working on the open heart, and in 1939 Laurence O'Shaughnessy[4] of the Lambeth Cardiovascular clinic in London wrote " ...... the real key to further advance in the surgical treatment of established cardiac defects will only be provided by the provision of some simple and efficient method of maintaining the cerebral circulation while the heart is temporarily out of commission".

The development and use of hypothermic techniques (Bigelow et al.,[5,6] 1950; Boerema et al.,[7] 1951; Delorme,[8] 1952; Ross,[9] 1954; Lynn et al.,[10] 1954; Gray,[11] 1955; Swan and Blount,[12] 1956;) was the first step towards the attainment of this goal, and on the 29th August, 1952, Bailey[13] performed the first open heart operation. The time limit when using this technique is such, however, that only relatively simple abnormalities, such as septal defects and certain valvular abnormalities can be corrected. In order to repair more complicated anatomical abnormalities, the heart must be excluded from the circulation for a longer period of time, and with this in mind experimental work continued.

The development of extra-corporeal pump-oxygenator systems (Bjork,[14] 1948; Gibbon,[15] 1939; Gibbon et al.,[16] 1954; Jongbloed,[17] 1949; Dennis et al.,[18] 1951; Melrose,[19] 1953; Dodrill et al.,[20] 1953; Mustard et al.,[21] 1954; Lillehei et al.,[22] 1956; DeWall et al.,[23] 1956; Kirklin et al.,[24] 1956; Kolff et al.,[25] 1956;) which allow temporary by-pass of the heart and lungs during intracardiac surgery provided the solution to the problem. The technique of total body perfusion has now been perfected, and the incentive to the surgeon to devise operative procedures for the correction of cardiac abnormalities has been provided. Yet still satisfactory techniques for the correction of all pathological types of mitral insufficiency have not been established.

It is the purpose of this investigation to study the incompetent mitral valve, with particular reference to problems in the design and testing of a suitable mobile prosthesis for the correction of this lesion.

HISTORICAL REVIEW

"The longer you look back, the further you can look forward", said Sir Winston Churchill[26] in an address before the Royal College of Physicians in March, 1944. By reviewing the past, gaps in our knowledge become clearly revealed, and the struggles, the failures and the successes of our predecessors, which have led to our present state of knowledge, become more fully appreciated.

That surgeons are today able to seriously contemplate the surgical correction of incompetent cardiac valves is possible only as a result of the work of those pioneers in cardiac surgery whose early endeavours in this field layed the foundation for future progress. A brief review of the development of the surgery of the heart, as well as a review of the past work on the correction of mitral insufficiency is thus an essential preliminary to our own study.

1. HISTORY OF THE TERM "VALVE".

The term "valve" was first used for the heart valves by Benedictus; the Greeks used the term "hymenes", while Vesalius named them "membranae". The bicuspid or left atrio-ventricular valve was named"mitral" by Vesalius because of its fancied resemblance to a Bishop's mitre. (Quain[27] 1929).

2. THE DEVELOPMENT OF SURGERY OF THE HEART.

It is just 63 years since a suture was first successfully placed in the pulsating human heart by Rehn[28] (1896) and the possibilities of cardiac surgery were realised.

The physicians of antiquity believed with Hippocrates[29] that injuries of the heart were necessarily fatal. "A severe wound of the bladder, of the brain, of the heart, of the diaphragm, of the small intestine, of the stomach and of the liver is deadly". (Aphorisms V1.18) For nearly 20 centuries the aphorism of the Coan physician was undisputed and this view was endorsed throughout the ages by poet and physician alike, until the middle of the 18th century.

In the Bradshaw Lecture of 1919, Sir Charles Ballance[30] gave a number of delightful references to injuries of the heart mentioned in the classics. The description by Sophocles of the death of Ajax following his falling on his sword; Homer's account of the movement of a weapon in the heart (when Alkathous was smitten by Idomeneus); the sudden death of Epanimondas at the battle of Mantinea, and of Sarpedon (wounded with a javelin by Patrohlas), immediately following the withdrawal of the weapons, are examples of the ancients knowledge of cardiac wounds and their fatality. Aristotle[31] (384-322 B.C.) said, "The heart alone of all viscera cannot withstand serious injury", and Galen[32] (130-200 A.D.) describing wounds in gladiators, pointed out that if a ventricle was wounded these gladiators died soon, and especially so if the left ventricle were wounded. Fallopius[33] (1523-1562) asserted, "Wounds of the heart are always followed by sudden death", and Boerhaave[34] (1668-1738 stated, "All wounds of the heart, deep enough to penetrate into either of its ventricles, are mortal".

The validity of this widely held belief was questioned by Hollerius[35] as early as the 16th century, and in 1604 Cabriolamas[36] first described two cases in which, at autopsy, he found undisputable evidence of previous cardiac injury, unrelated to the cause of death. He concluded that the heart is able to suffer a solution of continuity without death ensuing and this opinion was confirmed by Tourby[37] who in 1642, reported the finding of a myocardial scar at autopsy on a man who had had a sword thrust in the chest 4 years previously.

More than a century later, in 1761, Morgagni[38] first stressed the danger of compression of the heart from haemorrhage into the pericardial sac and in 1819 Romero[39] performed the first deliberate operation to drain the pericardium. Ten years later, Baron Larrey[40] (1829), Napoleon's surgeon, reported the successful management of a case of traumatic haemo-pericardium. He inserted a catheter through the stabwound and drained off 3 beakers of wine-coloured fluid. Following this success he wrote, "We venture to say that practitioners ...... have without any real grounds, taken too grave a view of the effects of wounds of this fibroserous envelope and are perhaps open to the same reproach respecting certain wounds of the heart".

It was not however until George Fischer[41] published his classic treatise on injuries of the heart in 1868, in which he recorded 452 cases with a 10% survival rate, that the medical profession was stimulated to seriously consider the possibilities of surgery in the treatment of cardiac disease.

With the introduction of anaesthesia in 1846 by William Thomas Morton[42], and of antiseptic surgery in 1865 by Lister[43], who based his work on the clear enunciation by Pasteur[44] of the theory that bacteria were a cause of disease, experimental surgical procedures began to be undertaken on animals. Becker[45], an opthalmologist, in 1872, in order to investigate the pulsation of the retinal vessels in aortic incompetence, was able to destroy one or more of the valve cusps experimentally in dogs, by inserting a glass rod down the left carotid artery. This investigator in turn refers to Quincke before him as having produced aortic regurgitation by tacking back an aortic cusp. Klebs[46] (1875) produced similar lesions using a "valvulotome" - a tiny knife on a long rod - which he inserted down the carotid arteries, and Cohnheim[47] (1877) using whale-bone sounds, Timofejew[48] (1888) using sounds and needles passed via the aorta and Rosenbach[49] (1889) using the "valvulotome" conducted similar experiments in order to study the haemodynamics of aortic regurgitation.

Meanwhile Block[50] in 1882 had successfully sutured lacerations made in the hearts of rabbits. A few years later first Reed[51] (1887), and then Dalton[52] (1891), each successfully repaired a wound of the pericardium and 13 years after Block's successful experiments Del Vecchio[53], at the meeting of the Eleventh International Medical Congress at Rome in 1895, demonstrated healed wounds of the heart, in dogs, following suture. Within a year Rehn[28] of Frankfort had performed the first successful operation on an human heart (9th September, 1896).

Despite the successes obtained during this period, medical opinion was divided on the merits of these newly introduced operations. Billroth[54], himself no timid surgeon wrote, in 1875, "Paracentesis of the pericardium is an operation which in my opinion, approaches very closely to that kind of intervention, which some surgeons would term a prostitution of the surgical art, and others madness.", and again in 1885[55], "Let no man who hopes to retain the respect of his medical bretheren dare to operate on the human heart". Later, Riedinger[56] in 1888 wrote, "The suggestion to suture a wound of the heart, although made in all seriousness, scarcely deserves mention", and Paget[57] (1896) unconvinced by the demonstration of Del Vecchio in the previous year stated, "Surgery of the heart has probably reached the limits set by Nature to all surgery; no new methods and no new discovery can overcome the natural difficulties that attend a wound of the heart".

Others however, were more optimistic. Weill[58] (1895) and Delorme[59] (1898) advocated the surgical treatment of constrictive pericarditis. Tuffier[60] (1897) successfully treated a case of cardiac arrest occuring during chloroform anaesthesia, by massaging the heart. In 1898, Samways[61] an English Veterinary surgeon first suggested the possibility of incising the mitral valve as a treatment for mitral stenosis and 4 years later Sir Lauder Brunton[62] (1902) published a "preliminary note on the possibility of treating mitral stenosis by surgical means".

The ensuing decade produced a vast amount of experimental work on the surgical treatment of valvular deformities. MacCallum and McClure[63] (1906) and Wiggers and du Bois[64] (1913) repeated and elaborated the earlier experiments of Klebs[46] and Cohnheim[47]. Haecker[65] (Germany) and Cushing and Branch[66] (America) almost simultaneously in 1907 reported the first series of experiments in which valves were cut in animals using a transthoracic approach. These reports were of great value in that they were the first to give hope that with improved techniques the risk of operation could be made almost negligible.

No new suggestions for the relief of valvular lesions were forthcoming until in 1913 Ernst Jeger[67] published his monograph, "Die Chirurgie du Blutgefasse und des Herzens", in which he suggested the use of venous shunts from the ventricle to the main vessel, as a means of overcoming valvular stenosis. In the same year Doyen[68] (1913) performed the first definitive intracardiac operation on a 20 year old female patient. His attempt to divide a stenosed pulmonary valve by inserting a small tenotome knife into the right ventricle was unsuccessful, and a post-mortem examination revealed a marked subvalvular narrowing rather than the localised stenosis that had been anticipated. Later that year Tuffier[69] (1913) successfully dilated the aortic ring in a patient with aortic stenosis, by invaginating the wall of the aorta just above the valve, and pushing the wall into the stenosis on the forefinger.

Almost a decade was to pass before a further attempt at surgery on the heart valves was made. In the interim the First World War (1914-1918) provided surgeons with experience in the treatment of wounds of the heart and it became obvious that the heart was able to tolerate manipulation and suturing.

The post-war years saw a revival of experimental cardiac surgery and in 1920 Cutler, Levine and Beck[70] commenced an investigation into the possibility of treating mitral stenosis by surgical means. Initial experiments to divide the stenosed mitral orifice under direct vision, by temporarliy occluding the great vessels, were unsuccessful, and the operation was abolished in favour of a blind approach through the left ventricle, using small knives on long handles.

In May 1923, Cutler[71] and Levine performed the first operation for mitral stenosis on an 11 year old female patient. Using a tenotome inserted through the left ventricle, an attempt was made to incise each cusp of the obstructing ring. This patient survived for 4½ years but 4 further operations during the next 2 years were unsuccessful.

Meanwhile in 1922 Allen and Graham[72] of St. Louis reported a new method of intracardiac surgery, using the cardioscope, an instrument rather like a female cystoscope, which enabled them to visualise the mitral valve. The following year Graham[72] attempted his first clinical case. The cardioscope was inserted into the left auricle but before any definitive surgical procedure could be carried out, the patient succumbed.

The first successful operation for mitral stenosis at which the fused commissures of the valve were digitally split, was performed by Sir Henry Souttar[73] in 1925. His original intention, to instrumentally divide the stenosed valve, was abandoned during the course of the operation, after he had passed his index finger through the valve orifice without encountering resistance, and to him must go the credit of having performed the first mitral commisurotomy.

Three further attempts at direct valvular surgery were made during the 1920's. Pribram[74] in November 1925 performed the operation of mitral valvotomy on a 28 year old female patient, using a cardiovalvulotome inserted via the left ventricle and Cutler and Beck[71] in November 1926 and again in April 1928, attempted to relieve a stenosed mitral valve also using the cardiovalvulotome; all three operations were unsuccessful.

The high mortality rate in these initial direct operations dissuaded surgeons from attempting further operations and no clinical progress was reported for 18 years, until Holmes Sellors[75] and Brock[76] in 1948 first described the technique of pulmonary valvotomy. During the same year Bailey[2] and Brock[3, 77] successfully performed the operation of mitral valvotomy, thus opening the modern era of direct attack on the heart valves. The previous year Smithy[78] (1947) himself a victim of the disease, had revived interest in the possibilities of the surgical treatment of aortic stenosis, and in the ensuing few years several reports dealing with blind digital and instrumental techniques via the aorta and left ventricle, to fracture or dilate the stenosed aortic valve, appeared in the literature. (Bailey[79, 80] 1950, 1952, Brock[81] 1950, Muller et al.,[82] 1954, Swann[83] 1954.)

Advances in the treatment of congenital cardiac abnormalities had been proceeding apace. Munro[84] in 1907, first suggested that cases of patent ductus arteriosus should be treated by ligation of that structure, and Graybiel et al.,[85] were the first to attempt the operation in 1938. The following year Gross[86] (1939) reported the first successful ligation and in 1947[87] recommended the present day method of treatment - that of excision and ligation. Crafoord[88] and Gross[89], independantly during 1948 introduced the surgical correction of coarctation of the aorta. The same year Blalock and Taussig[90] (1945) introduced their operation of systemic - pulmonary artery anastomosis for the treatment of the Tetralogy of Fallot; the following year Potts[91] (1946) suggested the easier operation of aortic - pulmonary artery anastomosis, and 2 years later Brock[76] performed the physiologically sounder operation of pulmonary valvotomy.

Murray[92] (1948) by introducing a strip of fascia lata into the right ventricle and attaching it to the septum, repaired an interventricular septal defect in man after animal experiments had demonstrated its possibility. He also first described a technique of closure of interatrial septal defects, by passing sutures through the anterior wall beginning to the right of the aorta and pulmonary artery, to emerge posteriorly between the superior vena cava and right pulmonary veins. The sutures were tied posteriorly, thus compressing the anterior and posterior walls of the atria. Cohn[93] (1947), and Swan[94] (1950) and Santy et al.,[95] (1950) devised methods for invaginating the atrial appendage or the lateral wall of an auricle to occlude a septal opening, and Gross et al.,[96] (1952) described the use of a rubber "atrial well", in order to correct such a defect.

Despite the advances which had been made by the middle of the 20th century, the cardiac surgeon was still hampered by his inability to visualise the operative field. The dangers and uncertainties of blind instrumentation and digital manipulations were realised and a suitable technique to allow of visualisation of intracardiac lesions was sorely needed. This was soon accomplished by the use of general hypothermia and inflow stasis, (Bigelow et al.,[5,6] 1950; Boerema,[7] 1951; Delorme,[8] 1952; Ross,[9] 1954; Lynn et al.,[10] 1954; Gray,[11] 1955; Swan and Blount,[12] 1956.) and in 1952 Lewis[97] performed the first open heart operation, the closure of an inter-atrial septal defect.

The limits of hypothermic techniques were soon exposed however and surgeons continued to search for a method which would allow them access to the open heart. Success was not long in coming and in 1953 Gibbon[98] performed the first successful open heart operation using a pump oxygenator. The heart and lungs were excluded completely from the patient's circulation for 25 minutes, and an interatrial septal defect was repaired. Two years later Melrose et al.,[99] (1955) advocated the use of potassium citrate for inducing cardiac arrest, thus enabling the surgeon to work within a still dry heart. The following year Effler et al.,[100] (1956) first employed the Melrose technique clinically, Lam[101] (1956) reported on the use of acetylcholine as a cardioplegic agent, and Lillehei et al.,[102] (1956) developed the technique of retrograde coronary sinus perfusion for direct vision surgery of the aortic valve.

Since the advent of extra-corporeal oxygenation two basic systems have proved successful in clinical application. In the one group are the biological oxygenator systems employing cross-circulation (Lillehei[103] 1955; Warden[104] 1954) heterologous (dog) lungs (Cambell[105] 1955), or a reservoir of oxygenated blood (Warden[106] 1955). In the other group are the artificial oxygenators employing one of three basic methods for extracorporeal arterialisation of venous blood. These are: (1) Bubble oxygenator in which oxygen is introduced directly into the venous blood (DeWall[23] 1956); (2) film oxygenator in which the red cells are also exposed directly to oxygen by being spread in thin layers over a large surface (Gibbon[107] 1951; Cross[108] 1956);

(3) membrane oxygenator in which oxygen and venous blood are exposed over a large surface separated by a suitable membrane, such as cellulose, which is permeable to oxygen and carbon dioxide (Kolff[25] 1956).

The interior of the heart, so long an important barrier to progress and the last anatomical frontier of the many that have confronted surgeons through the ages has at last been conquered utilising one of these methods of extracorporeal oxygenation. Many complex cardiac lesions, until a few years ago considered to be incurable, are now being treated surgically every day in centres throughout the world.

It remains for surgeons in the future to improve upon the methods of the present, and to devise new operations and techniques in order to repair those lesions which are to-day still incurable. As we progress, indirect procedures which can only, at best, bring about symptomatic improvement must be replaced by operations which restore structural and functional normality. In the words of Sir Russel Brock[109] in an address before the Henry Ford Hospital International Symposium on Cardiovascular Surgery in March 1955, "The future of all cardiac surgery must turn more and more toward direct and away from indirect surgery".

3. A REVIEW OF THE METHODS WHICH HAVE BEEN EMPLOYED FOR THE SURGICAL CORRECTION OF MITRAL INSUFFICIENCY.

Ever since 1948 stenotic lesions of the mitral valve have been satisfactorily treated by well-known surgical measures involving finger fracture supplemented in some patients by commissural incisions. Regurgitant lesions of the mitral valve, despite their clinical importance as a major cause of cardiac disability, have continued to challenge cardiac surgeons and numerous and diverse surgical approaches have been applied both experimentally and clinically. These may be divided into 5 main groups:

1. Operations involving the insertion of (a) tissue grafts or (b) a prosthesis within the chambers of the heart.
2. Operations involving the introduction of (a) tissue or (b) a prosthetic device between the valve leaflets.
3. Operations to distort, or decrease the circumference of the atrio-ventricular orifice.
4. Direct operations on the valve cusps, chordae tendiniae or papillary muscles.
5. Indirect operations.

1.(a) Operations involving the insertion of tissue grafts within the chambers of the heart.

Numerous operations, designed to compensate for a deficiency of valve substance have been reported in which tissue grafts, both mobile and fixed have been inserted within the chambers of the heart.

Murray, Wilkinson and MacKenzie[110] (1938) attempted to correct mitral regurgitation, experimentally produced in dogs, by the application of an inverted vein graft introduced through the anterior wall of the left ventricle by means of a cannula, and placed slackly across the ventricular cavity in the line of the resected cusp. The procedure aimed at the production of a flap-valve which would tamponade the mitral leak at each ventricular systole. Several animals survived the operation and their post-operative life was significantly longer than that of a control group. A modification of this method was later used for the treatment of mitral stenosis in 10 patients, with an operative mortality of 20%. (Murray[111, 112] 1950). The postero-lateral cusp was resected and an inverted vein graft threaded over a segment of tendon was placed across the valve orifice.

In 1952, Logan and Turner[113] reported having placed a sling of pericardium beneath the mitral valve in 11 human cases of mitral insufficiency, without operative mortality. All save 2 of their cases showed some improvement.

Prior to this Wilson[114], in 1930, in attempts to produce mitral stenosis in experimental animals, had studied the effects of placing a diaphragm of parietal pericardium with a small central aperture, cords of parietal pericardium, strips of fascia lata, and tendon with synovium intact, across the ventricular aspect of the mitral valve. He found that the method produced a satisfactory degree of obstruction to the flow of blood across the mitral valve, and that while fascia lata encouraged thrombus formation, parietal pericardium or tendon with synovium intact did not.

Numerous investigators have concluded however that free tissue grafts are unsuitable for the construction of a valve mechanism in the surgical treatment of cardiac disease. Templeton and Gibbon[115] (1949) used free grafts of pericardium and inverted vein segments to replace a cusp of the tricuspid valve in dogs. Although the graft functioned for a while, within a few weeks it became functionally inadequate because of fibrosis and shrinking. Bailey et al.,[116] (1951) repeated Murray's operation using both inverted vein and free pericardial grafts; they also noted fibrosis and shrinking of the graft. In a series of experiments on dogs Brewin[117] (1956) studied the use of a graft fashioned from a circular disc of homologous aortic arch suspended across the auricular aspect of the mitral valve on a strip of tendon. Post-mortem studies on these animals revealed that both the aortic tissue and the tendon had become contracted and fibrosed. Similar experiences have been recorded by Moore and Shumacher[118] (1953), Glover et al.,[119] (1953), and Tedeschi and Nahas[120] (1955).

In an attempt to preserve the blood supply of the transplanted tissue Bailey et al.,[116, 121] (1951, 1952) constructed a pedicled tubular pericardial graft. This was introduced through the wall of the left ventricle, made to pass between the chordae and the valve in proximity of the ostium and provided rhythmic valvular tamponade. (Bailey et al.,[122,123] 1952, 1954.) The placement of these grafts resulted in an high operative mortality (38% in 52 patients) and they became replaced partially by fibrous connective tissue and shrank to perhaps 2/3 of each former dimension. The newly created valvular action thus became abolished in time. Henderson et al.,[124] (1953) repeated this work experimentally, and confirmed that the pedicle grafts loose their blood supply and become shrunken and fibrosed. In view of this loss of function due to fibrosis and the high operative mortality the operation was abandoned.

The use of a non-mobile pedicled pericardial tube, placed diagonally across the posterior half of the valve orifice in close proximity to the mural cusp, was reported by Bailey et al.,[123] in 1954. This had the effect of adding new substance to the free edge of the posterior portion of the mural leaflet. The operation was performed on 7 patients with no operative deaths; regurgitation was abolished in 2 patients and significantly reduced in the remainder and all manifested definite clinical benefit. More recently Bakst and Loewe[125] (1957) and Bakst et al.,[126] (1958) described the experimental placement of a pericardial graft in the region of the posterior commissure and posterior half of the mural cusp, anchored below to the posterior papillary muscle. Post-mortem examination of animals sacrificed at 6 months, showed that the graft had in fact become completely fused to the posterior valve cusp.

Sakakibara[127] (1955) believing that elevation of the mural cusp would bring about competence of the valve by allowing the septal leaflet to approximate to it, placed an inverted vein graft threaded over 6 lengths of silk suture material below and behind that cusp. Twenty-seven cases were reported with 2 operative deaths. Follow-up studies after 8 months, on the first 10 patients revealed definite clinical improvement in 7 and all 10 were still alive.

Murray[128] (1956) placed homologous aortic valve transplants within the mitral ring of experimental animals. Each was anchored below by 3 tails to the ventricular myocardium, and above by 3 sutures via the atrial wall, just above the annulus. The grafts survived for up to 8 months in dogs and although showing microscopic degenerative changes, the cusps retained their form and function. The operation was then applied clinically; after transplantation there was no regurgitation and the effect post-operatively was quite satisfactory. The number of operations performed and the late results were however not reported.

Monk et al.,[129] (1958) in experiments on sheep, constructed an intra-atrial "baffle", by invaginating a portion of the auricular wall. This baffle which may be free, or fixed to the opposite atrial wall, lies across the auricular aspect of the mitral orifice, thus tending to decrease the degree of mitral regurgitation. This work is still in progress, but initial results are reported as being encouraging.

1.(b) <u>Operations involving the insertion of a prosthesis within the chambers of the heart.</u>

In view of the fibrosis and shrinking which tissue grafts undergo many prosthetic devices have been designed in an attempt to compensate for a deficiency of valve substance. Denton[130] (1950) described the use of a plastic cylinder with an opening in its posterior wall which was placed in the mitral orifice of experimental animals. During systole the contraction of the ventricular myocardium closed off the tube thus preventing regurgitation; during diastole blood flowed freely into the ventricle. Difficulty in anchoring this prosthesis however, caused Denton to abandon the method[131].

Carter et al.,[132] (1953) inserted a plastic ball ensheathed in a tube of pericardium between the mural leaflet of the mitral valve and the endocardial surface of the lateral ventricular wall of dogs, in an attempt to elevate this leaflet and provide a buttress against which the septal leaflet could close. Transauricular palpation confirmed the buttressing effect, but there was no indication that the dynamics of the valve had been changed. Post-mortem studies showed the pericardial tube to be thinned, avascular and collagenous, but there was no evidence of thrombosis or damage to the valve cusps.

Harken et al.,[133] (1954) and Harken[134] (1955) reported the use of a Lucite ball baffle, which was anchored on the ventricular myocardium beneath the mural leaflet of the mitral valve. Theoretically such a prosthesis should be moved by the myocardium into the deficient orifice during systole, and away during diastole. The operation was performed on 8 patients with unsatisfactory results due to the fact that the ventricle in mitral incompetence is grossly hypertrophied and dilated, and therefore spherical in shape, and the ball prosthesis was not moved across the valve orifice as expected. Autopsy however confirmed that the prosthesis was well tolerated and did not erode the myocardium. An essentially similar prosthesis was tested experimentally by Benichoux and Chalmot[135] (1955). The sphere was made of "plexiglass" and was held in place by a solid shank which protuded through the posterior ventricular wall. The operation was performed on 23 normal dogs; 12 survived for 2 months or more before being sacrificed. When performed on 10 dogs previously rendered incompetent however there were no survivors.

Under direct vision utilizing a pump oxygenator and using a right postero-lateral thoracotomy to approach the left atrium, Lillehei et al.,[136] (1958); Gott et al.,[137] (1957), employed a cylindrical Ivalon prosthesis for the correction of mitral insufficiency in a 43 year old female patient. A 4 cm. long, 15 mm. diameter cylinder of compressed Ivalon (4 : 1) was sutured to the annulus of the scarred and contracted mural leaflet, thus replacing the lost substance normally provided by that leaflet, and providing a firm buttress against which the septal leaflet was able to approximate during systole. Satisfactory clinical results using this operation have since been reported by Barnard, McKenzie et al.,[138] (1959); Ellis et al.,[139] (1959); and Barnard, McKenzie and Schrire[140] (1960).

Mobile prostheses have also been used in the attack on the incompetent mitral valve. Carter et al.,[132] (1953) employed a plastic ball, covered with pericardium and slung within the ventricular cavity, which flapped as a ball-valve. In 8 experiments only 1 animal survived. Johns and Blalock[141] (1954) performed a series of experiments using a mobile prosthesis, suspended across the ventricular portion of the mitral valve orifice between the commissures and parallel to the opposing edges of the valve leaflets. The ends of the prothesis were pulled through the myocardium at the apices of the two papillary muscles and anchored to the epicardial surface of the heart. Of the prostheses studied - polyvinyl sponge (Ivalon), pericardial sacs filled with blood or plastic material, segments of inverted vein filled with blood or plastic, polyethyline film fashioned into sacs - Ivalon was found to be the most satisfactory, and in all animals at sacrifice, was covered with endocardium and was still mobile. There were 20 survivors in 30 experiments and 2 of these dogs had survived 11 and 12 months at the time of the above report.

Jordan and Wible[142] (1955) experimentally in dogs inserted a "Y" shaped spring steel (Elgiloy) frame, covered with nylon, via the posterior wall of the left ventricle, so that it came to lie below the valve orifice. During systole the prosthesis was forced upwards towards the atrium, thus effectively closing the mitral orifice; during diastole it returned to its position of rest and blood flowed into the ventricle. The prosthesis was well tolerated, the nylon becoming covered with endothelial-like cells and experimental animals survived for up to 5½ months. The technique was then employed clinically and in 1957[143] these authors reported a successful case with a one-year follow-up.

Berg et al.,[144] (1957) devised an artificial valve consisting of a ring, which was fixed to the mitral annulus, and a central hinged flap. Valves fashioned from several plastic substances (type not stated) were tested but it was found that they were not durable and favoured clot formation. A stainless steel valve was then inserted, and although associated with a large early mortality, survivors lived longer than a group in which a similar, but plastic valve, had been used.

Kernan et al.,[145] (1957) described an artificial valve consisting of a Teflon shell housing a solid methyl methacrylate (Lucite) sphere, to replace the incompetent mitral valve. The valve was inserted under direct vision, utilising a pump-oxygenator and elective ventricular fibrillation. Twenty-five such operations were performed on dogs, and, although the prosthesis appeared to be mechanically satisfactory there was only 1 long term survivor (4 months).

Ellis and Bulbulian[146] (1958) in animal experiments have attempted to insert a Lucite ball valve, or a Teflon valve employing a free floating disc on a central spindle, in place of the normal valve. Five experiments were performed the longest survival being 6 days. Post-mortem examination in 3 animals revealed that the entire mitral orifice was occluded by thrombus and the authors concluded that Lucite and Teflon are not suitable materials for use in the fabrication of a prosthetic mitral valve, because of their tendency to initiate clot formation in this location.

2.(a) Operations involving the introduction of tissue between the valve leaflets.

The observation, that the regurgitant jet of blood felt by the exploring finger at the time of mitral commissurotomy in patients with combined stenotic and regurgitant lesions can usually be completely occluded by the exploring finger, so that there is temporarily complete competence of the valve, suggested that a tubular structure, introduced through the insufficient portion of the valve orifice so that the valve edges might approximate against this structure during systole, would control the regurgitation. The results obtained by previous workers[116, 118, 124] also indicated that to be successful a tissue graft should be well vascularised.

Utilising this concept Glenn et al.,([147] 1954, [148] 1955) performed a series of experiments on dogs. A 10cm. length of external jugular vein was excised and sewn to the edges of an incision in the wall of the left auricle. The left internal mammary artery and vein, together with a perivascular cuff of connective tissue, were dissected free, ligated and divided at the level of the 8th interspace, and drawn through the segment of vein, which was inverted and pulled through the mitral orifice, into the ventricle and anchored to the ventricular myocardium. In 23 experiments there were only 5 deaths; 9 animals were sacrificed at periods ranging from 10 to 32 weeks, and neither the grafts nor the valve cusps showed any evidence of major damage. The operation was then performed on 3 patients, but for purely technical reasons, failed to control, although it relieved the regurgitation (Glenn et al.,[149] 1956).

Bailey et al.,[150] (1955) described the use of a transvalvular vertically suspended stent for the control of mitral regurgitation. A cone-shaped section of costal cartilage was covered with pericardium and suspended by pericardial tails, anchored to the atrium superiorly and the ventricle inferiorly, between the leaflets of the mitral valve, the broad end of the wedge towards the atrium. The operation was performed on 3 patients with considerable improvement in each case.

Plugging of the incompetent area of the valve orifice by inversion of the left auricular appendage or vascularised atrial flaps has also been advocated. Hayward[151] (1953) invaginated the left auricular appendage through the mitral valve and attached it to the ventricular myocardium under the mural cusp. Only 2 operations were performed and in each, although early results appeared encouraging there was deterioration within 3 months of the operation. Hayward also suggested an operation envisaging invagination of all except the tip of the appendage. The tip would then remain right side out as a conical projection, like a paper hat inside the invaginated portion fixed to the ventricular wall along its outer margin. During diastole it should remain flattened and empty causing minimal obstruction to the flow of blood from auricle to ventricle. During systole it should balloon with blood and its inner part should make contact with the aortic cusp and close the orifice.

Botwin[152] (1954), in experiments on dogs, fashioned a pedunculated atrial flap which was pulled via the mitral orifice into the ventricle and through the posterior ventricular wall immediately adjacent to the septum. Early results were satisfactory but the flap soon became shrunken and fibrotic, and regurgitation recurred. The atrophy of such flaps was confirmed by Shumway and Lewis[153] (1954) who, in experiments on dogs under direct vision utilising hypothermia, sutured atrial pedicles to either papillary muscle in an attempt to correct mitral insufficiency. Animals sacrificed as early as the 6th postoperative week showed atrophy of the flaps.

2.(b) <u>Operations involving the introduction of a prosthetic device between the valve leaflets.</u>

In view of the unsatisfactory results obtained when using tissue grafts, which almost invariably become shrunken and fibrosed when placed within the cavities of the heart, several investigators have employed one or other non-viable transvalvular prosthesis in attempts to correct mitral insufficiency.

Harken et al.,[133] (1954) and Harken[134] (1955) designed a Lucite prosthesis in the shape of a bottle, which was anchored above and below the antero-lateral aspect of the annulus, its neck engaging either under the mid portion of the aortic leaflet or under the postero-medial fringe of leaflet insertion on the annulus. Twenty-four terminal patients with mitral insufficiency were operated on using this procedure; there were 7 operative and 7 late deaths. Of the surviving 10 patients, 8 were reported as being substantially improved. The difficulty of inserting the prosthesis in the optimal position and the inconstancy of the position maintained by the baffle, rendered this operation unsatisfactory and a technique was next evolved for placing a Lucite spindle baffle through the mitral orifice, so that its position was maintained. The narrow end of the spindle was placed beneath the annulus, against the ventricular myocardium (at the site of minimal regurgitation which is most commonly anteriorly) and the broader extremity was brought up through the orifice and fixed postero-medially just above the annulus, the prosthesis thus coming to lie obliquely through the mitral valve. This prosthesis does not interfere with leaflet mobility and its position ensures supplementation of leaflet deficiency regardless of changes in size of the annulus and/or the ventricle. Twenty-nine operations were performed with only 10 survivors, whose progress was reported as "encouraging".

Glenn et al.,[149] (1956) studied the effects of a cylindrical segment of polyvinyl (Ivalon) sponge suspended between the mitral valve cusps, of experimental animals. The prosthesis was anchored to the dome of the atrium above and to the myocardium of the left ventricle, near the apex, below. It had previously been demonstrated[141] that this substance, placed across the chamber of the left ventricle, was well tolerated, and that the invasion by fibroblasts ultimately resulted in complete coverage of the prosthesis. There were only 5 deaths in 34 experiments and the method was then applied clinically in 3 patients. There was 1 early post-operative death (cause unknown), 1 patient was no better a year after operation, and the remaining patient was slightly improved when seen 11 months later.

DeWall et al.,[154] (1956) used an Ivalon sponge prosthesis to straddle the posterior commissure of the mitral valve, in a series of experiments on dogs. Two designs of prosthesis were tested. The first was fusiform in shape and constructed so that its maximum diameter would lie at the annulus. Later, to minimise the amount of obturator within the atrium, an inverted cone-shaped prosthesis was employed, its apex fixed to the posterior papillary muscle, and its base constructed to lie at the level of the annulus. A narrow protusion of sponge extended from the base of the cone and was placed across the posterior commissure, to serve as the atrial attachment of the prosthesis. It was found that while the fusiform prosthesis was well tolerated, the conical was not, and clots tended to form on its base. Also, the Ivalon contracted and was shaped as the pressure of the mitral leaflets dictated, and thus any area of valve deficiency that was present tended to become filled. On the basis of their experimental results these authors concluded that this technique could be applied clinically; they however did not report having performed any operations on humans.

Rumel and Cutler[155] (1958) designed an Ivalon prosthesis consisting of a wedge-shaped body and 3 tails. Using a blind technique the prosthesis was placed between the valve leaflets, the apex of the wedge pointing towards the atrium, and was anchored to the walls of the atrium and the ventricle by means of the 3 tails. Experimental animals tolerated the introduction of the prosthesis remarkably well, and the method was then applied clinically. Five operations were performed, with 1 death due to postoperative haemorrhage. In all these patients it was estimated at operation that 75% or more of the regurgitant jet had been abolished, and in view of their initial favourable results, these authors consider that further limited clinical application is justified.

3. Operations to distort, or decrease the circumference of the atrio-ventricular orifice.

The techniques already described have, in common, the aim of providing additional substance (tissue graft or prosthesis) to compensate for a deficiency (absolute or relative) of valvular tissue. Theoretically the same end result could be achieved by decreasing the area of the valve orifice, and, provided that any such narrowing is not excessive, stenosis will not be produced. (Gorlin and Gorlin[156] 1951). Several operations have been devised in an attempt to correct mitral insufficiency, utilising this concept.

Bailey et al.,[121] (1951) described an operation to narrow the effective atrio-ventricular orifice by encircling 80% of the chordae tendiniae attached to the 2 cusps with a strip of fascia lata, and anchoring the ends of the latter to the ventricular myocardium. The operation was applied clinically but the results were not stated. A similar operation, using a silk ligature dipped in boiling vaseline had been performed by Cushing[66] in 1907 in an attempt to produce mitral stenosis in experimental animals. Cushing was unable to secure a survivor but Bernheim[157] (1909) repeated the experiment on 30 dogs with 10 survivors. More recently Shaw et al.,[158] (1942) and Connelly[159] (1950) have described similar experiments.

Hurwitt et al., ([160] 1954 and [161] 1955) in an attempt to decrease the circumference of the atrio-ventricular ring excised a vertical wedge of myocardium, extending for about 2/3 of the thickness of the ventricular wall. Two Lembert sutures placed parallel to the circumflex coronary artery and to each other, were used to approximate the edges of the incision, with a resultant decrease in the circumference of the mitral annulus. Initial experimental results were encouraging and the operation was therefore applied clinically. Only 1 operation was performed, and the degree of regurgitation was unchanged postoperatively. This operation also had been previously performed (experimentally, with survival) by Carrel[162] in 1910.

In order to produce mitral stenosis in dogs, McAllister and Fitzpatrick[163] (1956) developed a technique to constrict the mitral valve orifice using a purse-string ligature tied around the atrio-ventricular sulcus. In 1954 the technique was applied as a desperate measure to control mitral regurgitation while operating on a poor-risk patient, erroneously diagnosed as suffering from mitral stenosis. Late results in this patient were encouraging and the operation was then re-applied in the experimental laboratory. The method used entailed the passage of a tape ligature through the right auricle, the 2 ends of the tape being tied in the atrio-ventricular sulcus. Such a ligature lies approximately 4 mm. above the true annulus, the intracardiac portion becoming endothelialised and the remainder embedded in the interatrial septum and the atrio-ventricular groove. The operation was later performed on 2 patients as an elective procedure but neither patient was improved. Similar operations to produce experimental mitral stenosis have been recorded by Ellison et al.,[164] (1952) using a steel suture covered with nylon tubing, and Borrie[165] (1953) using a floss silk ligature, both with satisfactory results.

Davila et al., ([166] 1954, [167] 1955, [168] 1957.) and Glover et al., ([169] 1955, [170] 1957, [171] 1957.) carried out extensive experimental investigations and clinical trials utilising a circumferential purse-string suture for the correction of mitral insufficiency. A suture of braided silk or braided cotton tape was placed around the atrio-ventricular ring, below the circumflex coronary vessels and passed via the right atrium adjacent to the right side of the interatrial septum. That portion of the suture which lay within the transverse sinus was encased in a pericardial sleeve, thus preventing the suture from eroding into the lumen of the left atrium. Initial experimental results in 150 dogs were highly satisfactory and the method was then applied clinically. The results of the first 61 operations were reported by Davila[172] in 1958. There were 18 operative deaths, 13 late deaths and 30 survivors. Thirty-two of the patients were in a reasonable condition pre-operatively, that is in congestive failure clinically correctable, and of these 26 were alive and improved at the time of the report.

Using the Davila-Glover technique Kent et al.,[173] (1958) performed 30 operations with only 11 survivors, and in 7 of these survivors insufficiency recurred within days, weeks or months, and Besher[174] (1958) performed 6 operations with 2 survivors, in one of whom insufficiency recurred.

Bailey et al.,[150] (1955) dissected the fat pad, along with the circumflex coronary artery and coronary sinus, from the atrio-ventricular groove, displaced these structures downwards, and plicated the mitral annulus with a series of interlocking silk mattress sutures, the long axis of each suture being placed parallel with the fibres of the annulus. The operation was performed on 3 patients with severe mitral insufficiency, and in each the regurgitation was reduced by approximately 50%.

Kay and Cross[175, 176] (1955) observing that the regurgitant jet of blood in mitral insufficiency is usually maximal at the postero-medial commissure, performed a series of experiments in an attempt to devise a technique which would reduce the size of the mitral ring at this area. This in turn would allow approximation of the edges of the valve leaflets and obliteration of the incompetent space. The technique adopted, which was similar to that employed by Ferrin et al.,[177] (1951) to produce experimental mitral stenosis, entailed the blind introduction of a double silk suture at the junction of the aorta and auricles, through the anterior and posterior segments of the mitral ring adjacent to the posterior commissure, and out the ventricular side of the coronary sinus in the region free of the circumflex coronary artery posteriorly. This suture was drawn taut, approximating the anterior and posterior segments of the mitral ring as determined by an intracardiac finger, and tied over buttons of cartilage. The operation was performed on 4 patients; 1 patient died as a result of the operation and the remaining 3 were significantly improved.

Nichols[178] in 1957, described the operation of "polar cross-fusion of the mitral annulus" which is essentially similar to that performed by Kay and Cross. A heavy Dacron suture, ensheathed with a strip of pericardium, is placed around the septal and mural portions of the mitral annulus at the posterior commissure, drawn taut and tied. The opposing portions of the annulus are thereby approximated one to the other. Actual physical contact of the two opposed points upon the annulus, is considered imperative to the success of the procedure, and Gilman et al.,[179] (1957) have shown, that after 3 weeks a fibrous bridge has formed, which is strong enough to hold the edges of the approximated annulus without the presence of the suture. After initial animal experiments, Nichols applied the operation clinically. Thirty-seven patients were operated upon with an operative mortality of 14.7%. The regurgitant jet was completely abolished in 16 of the survivors and significantly reduced in the remaining 17.

Annuloplasty, under direct vision utilising extra-corporeal oxygenation, was recently described by Lillehei et al., ([180, 181] 1957, [136] 1958.) and Gott et al.,[137] 1957. The orificial circumference was reduced by placing interrupted silk mattress sutures in the annulus fibrosus at the insufficient area, and tying the latter over pillows of compressed Ivalon sponge, to prevent any possibility of their cutting out. After initial animal experiments the operation was performed on 4 patients, with 3 "excellent" and 1 "good" result. Merendino and Bruce[182] (1957), and Merindino et al.,[183] (1959), performed an identical operation on 4 patients; 1 patient died and the remaining 3 were alive and well, with no signs of residual regurgitation, at the time of publication.

An essentially similar operation of annuloplasty under direct vision, utilising extracorporeal oxygenation and induced cardiac arrest was reported by Scott et al.,[184] (1958). Five operations were performed with 3 survivors.

Kay et al.,[185] (1958) described a method of plicating the annulus under direct vision, using linear sutures placed in the anterior and posterior limb of the mitral annulus, above and below the postero-medial commissure, in order to approximate the cusps of the incompetent valve. In some cases it was necessary to plicate the annulus at the antero-lateral commissure or at both commissures; in others, linear plication at multiple points around the circumference of the annulus was necessary. Occasionally, a plug of Ivalon sponge was inserted, to fill the reduced space between the limb of the annulus at the site of plication, when complete approximation produced an undesirable amount of restriction at the orifice. Thirteen operations were reported with only 1 death. The remaining 12 patients all showed improvement when examined between 2 and 8 months post-operatively.

Harken[134] (1955) noted that external pressure over the incompetent postero-medial commissure of the mitral valve frequently reduces the regurgitant jet. He therefore attempted to correct mitral insufficiency by placing a roll of "Gelfoam" or other extrinsic baffle to maintain such pressure. The procedure was used in mild cases and appeared to function satisfactorily, but the long-term results were not reported. Robertson[186] (1955) similarly distorted the mitral annulus in 2 patients, using a pedicle flap of pericardium, which was rolled up into a ball and sutured to the outer surface of the heart over the annulus, and more recently Conklin et al.,[187] (1959) have reported on the use of an Ivalon sponge pack to maintain the annular distortion. Both authors report gratifying clinical successes.

Kuykendall et al.,[188] (1958) described a technique for the correction of experimentally induced chronic mitral regurgitation[189] in dogs, by the use of a double heavy-braided silk distorting or reefing suture, placed in the posterior portion of the mitral annulus. Such a suture, tied over two Ivalon covered plastic buttons placed just posterior to the anterior descending coronary vessels and just anterior to the posterior descending coronary vessels respectively, results in an inward bulging of the posterior portion of the annulus, thereby narrowing the mitral ring. Although initial experimental results were satisfactory these authors do not recommend the clinical use of this operation at this time.

4. <u>Direct operations on the valve cusps, chordae tendineae or papillary muscles.</u>

Several operations have been employed both experimentally and clinically which involve some direct manipulation of the valve cusps, chordae tendineae or papillary muscles.

Bailey et al.,([122] 1952 [123] 1954) and Bolton et al.,[190] (1953) described the operation of mitral commissurorrhaphy at which the lips of the incompetent portion of the valve are sutured together using a strip of pericardium or inverted vein segment as the suture material. Passed blindly through the apex of the left ventricle into the ventricular cavity, and guided by an intracardiac finger, the suture was caused to penetrate a selected point in each valve leaflet, and the ends of the suture were anchored to either the atrial or ventricular myocardium. Later, a simple "hangman's noose" principle was employed to tighten the suture and thus approximate the valve edges, the single end being anchored as before. This general technique was used in 72 operations with an operative mortality of 27,8%[123].

In 1953 Jamison and Bakst[191] developed an instument, the mitral stitcher, designed to permit suturing of the mitral valve by a purely trans-atrial approach. Using pericardium or vein segments as suture material and employing the Gemeimhardt[192] pump to support the systemic circulation during the intra-cardiac manipulations, 25 operations were performed with a mortality of 16%.

More recently Effler et al.,[193] (1958) have approximated the valve leaflets of the incompetent portion of the valve by direct suture under vision utilising a pump-oxygenator.. The valve is then buttressed from the atrial side by a crescent-shaped Ivalon prosthesis sutured in place, both to the annulus and to the underlying valve leaflets. Such reinforcement appears to be essential when performing direct valve suture as Lyons and Kirklin[194] (1957) have shown experimentally that unsupported sutures may tear through acutely within 24 hours or more gradually within 3 weeks.

Attempts have been made to shorten the longer chordae, or lengthen the shorter ones in cases of valvular incompetence due to differential shortening of the chordae suspending the respective leaflets. The former approach was employed by Bailey et al.,[122] (1952) and Bolton et al.,[190] (1953) who devised a technique of "valvular suspension" in an attempt to encourage valvular approximation during systole. A pericardial strip or inverted vein segment was passed through the ventricular wall, through the septal leaflet and back out through the ventricular wall. This had the effect of a double or inverted "U" chordae tendineae, to pull the septal leaflet downward and laterally. The technique was used in 3 cases, and excellent immediate results were reported. Later Jamison[195] (1954) modified this technique so that the leaflet was not suspended by a suture about the free edge but by a transvalvular pericardial strip, with a terminal knot, which being too large to penetrate the perforation in the valve cusp, came to lie upon its atrial aspect.

The latter approach was employed clinically by Dodrill[196] (1954) who attempted to detach acquired adherence between the papillary system and the ventricular wall by transvalvular digital separation, and by Johnson[197] (1956) who employed a finger ring-elevator, introduced via the left auricle, to stretch the chordae of the mural cusp in the region of valvular incompetence. The edge of the elevated posterior mitral leaflet was then sutured to an invaginated portion of the posterior atrial wall, a semirigid reinforced posterior leaflet thus being constructed. This procedure is essentially a modification of Albanese's[198] operation atrio-commissuropexy, described in 1955. Johnson reported 5 "good" and 1 "fair" result in 6 operations.

Shumway and Lewis[153] (1954) in experiments on dogs, attempted to lengthen the chordae by excising either papillary muscle with the chordae attached and resuturing that divot nearer the atrio-ventricular ring. Eight operations were performed but there were no survivors. In order to increase the mobility of the valve, the mural cusp was detached from the posterior valve ring by an incision just above the junction between leaflet and mitral ring. Dissection downwards into the thick ventricular wall mobilised a large segment of tissue from the postero-lateral commissure to the aortic leaflet. There were 3 operative deaths in 12 experiments, and although the operation was temporarily effective in producing mobilization, the processes of healing soon nullified this effect.

5. Indirect operations.

Rappaport et al.,[199] (1948) suggested that an anastomosis, with valvular properties, between the left atrium and ventricle, would serve as a safety valve, guarding against a rising atrial pressure in mitral insufficiency. They therefore performed an anastomosis between the left auricular appendage and the ventricular cavity in experimental animals. Theoretically, because of the funnel shape of the appendage, blood should flow from a broad base at the atrium to a narrow apex at the ventricle, whereas back-flow through this structure would be difficult. Thirteen experiments were performed with 1 death, and the theoretical prediction was confirmed. The late results of these experiments were not reported however.

The pathological anatomy of many cases of serious mitral valve regurgitation is such that there is "virtually fibrous ankylosis of the valve mechanism" (Brock[200] 1952). Monk et al.,[129] (1958) pointed out that no mechanical contrivance devised has been really successful and they considered it unlikely that the disordered anatomy of such a valve could ever be restored by any means known at that time. They therefore suggested that the disordered haemodynamics associated with mitral regurgitation could be altered favourably by indirect methods.

When mitral regurgitation results from any cause, part of the stroke volume at each ventricular systole is driven backwards into the atrium and its entering veins, with resultant enlargement of the atrium and pulmonary congestion, and a reduction of the effective cardiac output into the aorta. X-ray screening in such cases often reveals left atrial pulsation that is synchronous with ventricular contraction, and it is obvious that a great deal of kinetic energy is being expended uselessly in this way. If the left atrium of such a patient were to be reduced in size and rendered almost inexpansible, and at the same time back-flow into the pulmonary veins reduced, this kinetic energy would be conserved and forward cardiac output promoted.

Utilising this concept experiments were performed in sheep to change the direction, the shape, or the size of the lumen of the entering veins, in order to reduce the back-flow during systole, without interfering with forward flow during diastole. These manoeuvres were performed on the vena cavae, after tricuspid insufficiency had been produced, and post-operative observations suggested that back-flow had been reduced. Similar operations were not possible on the pulmonary veins, because of the small size of these vessels in sheep, but would be possible in humans. Monk and his colleagues report that they intend performing hydrostatic experiments using cadaver material to assess the effectiveness of this method when applied to the left side of the heart.

Any indirect operation however falls far short of the goal of restoring anatomical normality, and at best could be applied only as a means of palliation.

THE SURGICAL AND PATHOLOGICAL ANATOMY OF THE MITRAL VALVE

Since the advent of techniques of extracorporeal oxygenation direct vision surgery of the mitral valve has become possible. Knowledge of the anatomy and function of the normal and the abnormal valve has thus assumed a new practical importance, as it is only when armed with this knowledge that an intelligent attack on the diseased valve can be made by the surgeon.

1. THE ANATOMY OF THE NORMAL MITRAL VALVE[27, 201, 202, 203].

The normal mitral valve apparatus consists of four parts: the annulus fibrosus, the valve cusps, the chordae tendineae, and the papillary muscles.

(i) The Annulus Fibrosus.

The mitral annulus fibrosus - an important part of the "skeleton of the heart" (Tandler[204] 1913) - is formed by the fibrous tissue surrounding the left atrio-ventricular orifice, which is not in the form of a uniformly developed ring-like band, but consists of parts of very different consistency and structure. (Fig. 1). Thus its left and posterior segments consist of loose fibrous tissue, while its right and anterior segments are formed by the adjacent portions of the dense fibrous and almost cartilaginous-like trigona fibrosa (dextrum and sinistrum) and of the fila coronaria (medium and sinistrum) which pass from them.

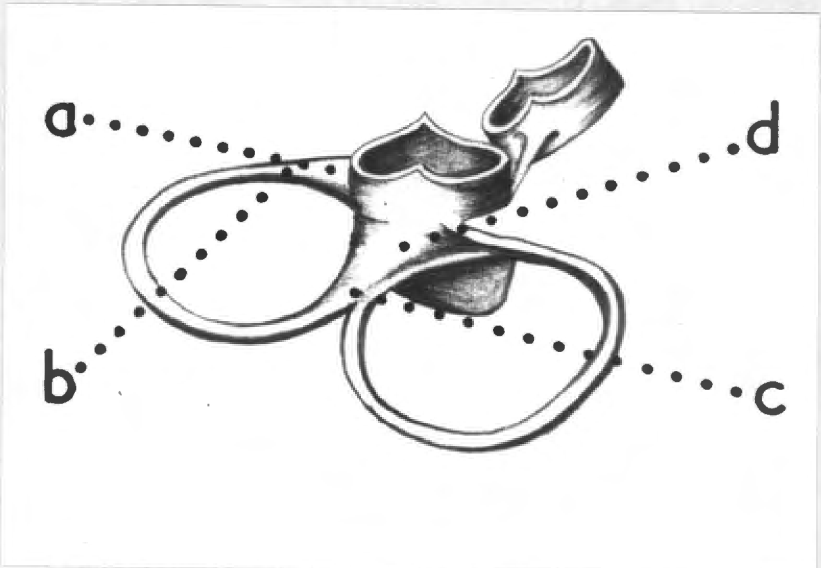


FIGURE 1. The skeleton of the heart.
a and d - Trigona fibrosa sinistrum and dextrum.
b and c - Fila coronaria sinistrum and medium.

The annulus represents the dividing line between the atrial and ventricular musculature from the eighth week of intrauterine life on, and appears in the embryonic heart as a result of the crowding together of the connective tissue framework of the organ (Gould[205] 1953). Its upper border is the point of origin of atrial muscle fibres and its lower border is the point of origin of the ventricular musculature; its internal circumference serves for the attachment of the valve leaflets and its outer aspect constitutes the deepest part of the atrio-ventricular groove on the external surface of the heart. A periannular space occupied by epicardial fat and loose connective tissue, which may be readily demonstrated by sectioning the ring radially at various points, courses around the ring throughout its circumference and separates the vascular structures from the valve-ring proper.

A detailed study of the relations of the mitral ring has been carried out by Davila et al.,[166] (1954), who arbitrarily divide this structure into 3 zones:

(a) A medial zone intimately related to the left coronary artery, the aorta and the aortic valve, the base of the interatrial septum, the top of the interventricular septum, the tricuspid valve ring and the coronary sinus.

(b) An antero-lateral zone related to the proximal portion of the circumflex coronary artery and the terminal portion of the great cardiac vein.

(c) A postero-lateral zone related to terminal branches of the circumflex coronary artery, the proximal portion of the great cardiac vein and the coronary sinus.

van der Spuy[206] (1958) has recently pointed out that, as the base of the antero-medial cusp is attached to the origin from the aortic root of two adjacent aortic cusps (Walmsley[207] 1958), the antero-medial half of the valve ring is bi-concave; (Figs. 2 and 3) as the base of the postero-lateral cusp is attached to the concave base of the left ventricle, the shape of the posterior half of the mitral ring is semi-ovoid. Because of the common origin of the antero-medial mitral leaflet and 2 adjacent aortic leaflets, the antero-medial sector of the valve ring is convex posteriorly, and the mitral ring as seen from above is somewhat reniform in outline.

The circumference of the valve orifice may be most accurately measured by passing graduated wooden cones. Quain[27] (1929) and Chiechi et al.,[208] (1956) using this method, found the average size of the adult male left atrio-ventricular orifice at autopsy to be 122 mms. and 100 mms. respectively. Measuring the circumference of the ring in the opened heart at autopsy, Rusted et al.,[209] (1952) found the average length to be 99mms. In each series, the size of the ring in the female heart was found to be slightly smaller than that of the male.

During life the atrio-ventricular orifice is not circular in shape and its surface area can therefore be only roughly estimated.

FIGURE 2. The antero-medial mitral leaflet as seen from the left ventricle. The common origin of the antero-medial mitral and two adjacent aortic valve cusps from the bi-concave mitral annulus is shown.

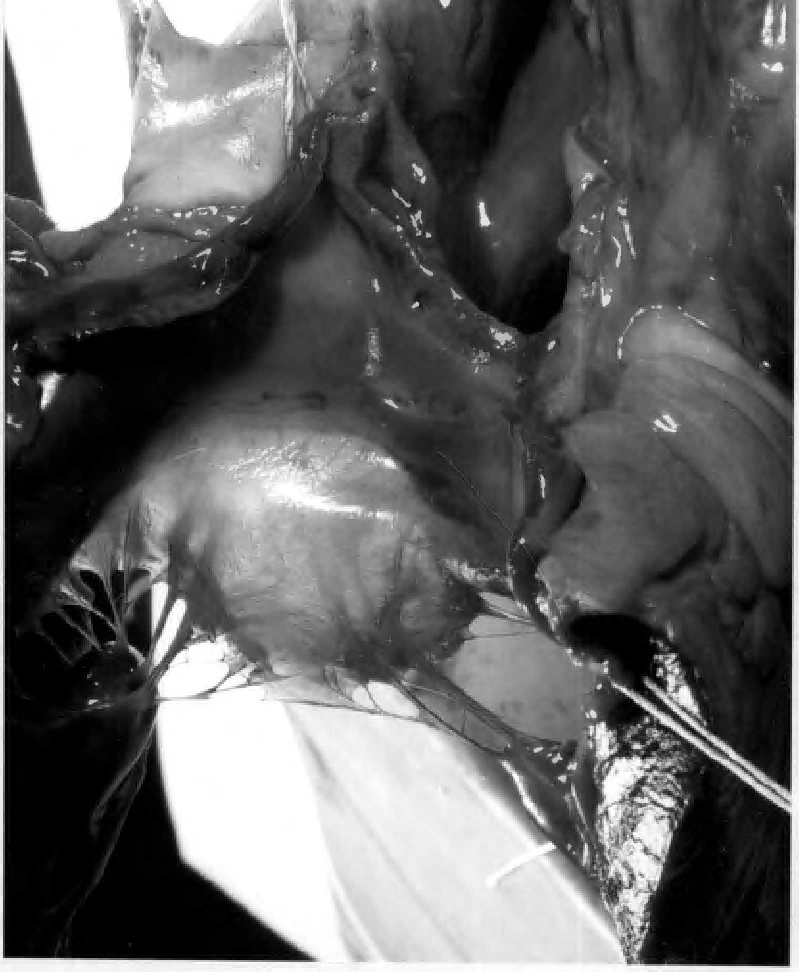


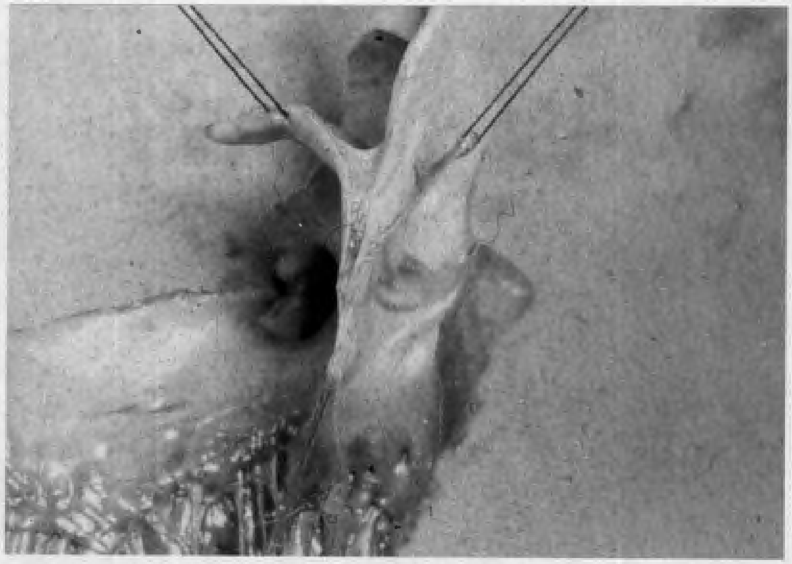
FIGURE 3. The antero-medial mitral leaflet as seen from the left atrium.

Average figures quoted are 855 sq. mms. (Quain [27] 1929) and 793 sq. mms. (Chiechi et al.,[208] 1956) for the male heart, and slightly less for the female.

(ii) <u>The Valve Cusps.</u>

The mitral valve is represented by a continuous veil of valvular tissue attached as a muff to the entire circumference of the atrio-ventricular annulus. The free edge of this muff projects into the ventricular cavity and is split by indentations,(Fig. 5) none of which reach the annulus, and which divide the valvular tissue into two major leaflets or cusps. These are located antero-medially and postero-laterally, the major axis of the mitral orifice consequently being directed obliquely forwards from right to left.

The antero-medial leaflet (aortic, septal or greater leaflet) (Figs. 2,3,7.) is the most important from the anatomic as well as the physiologic standpoint. It is the only dividing structure between the aortic and mitral orifices (Fig. 4) and constitutes an intergral part of the left ventricular out-flow tract. In shape it is roughly triangular with a blunted apex. The average length of the attached edge of the cusp and the average height from apex to attached margin, in normal male hearts examined at autopsy was found by Chiechi et al.,[208] (1956) to be 37mms. and 24mms. respectively; the average surface area was equal to almost one half the average total valvular-tissue surface area (1398 sq. mms.)



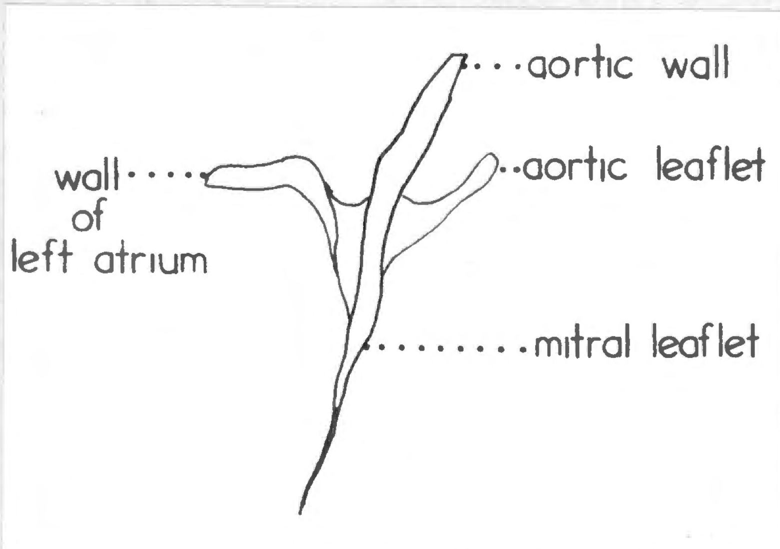


__FIGURE 4.__ Photograph and diagram of a vertical section through the root of the aorta and the antero-medial mitral leaflet.

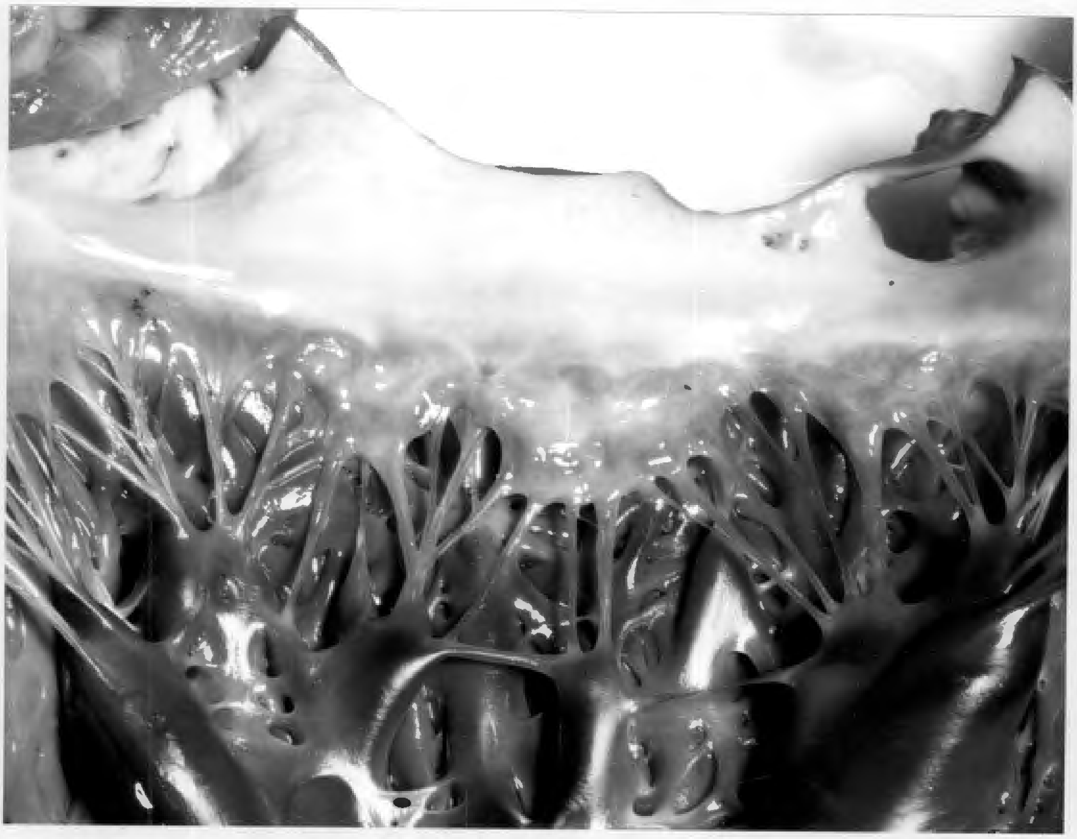


FIGURE 5. Photograph showing the atrial surface of the irregularly quadrangular postero-lateral mitral leaflet; no chordae attach to this surface which is perfectly smooth and the cusp appears to be a continuation of the atrial wall. Note the triple postero-medial and the single grooved antero-lateral papillary muscle.

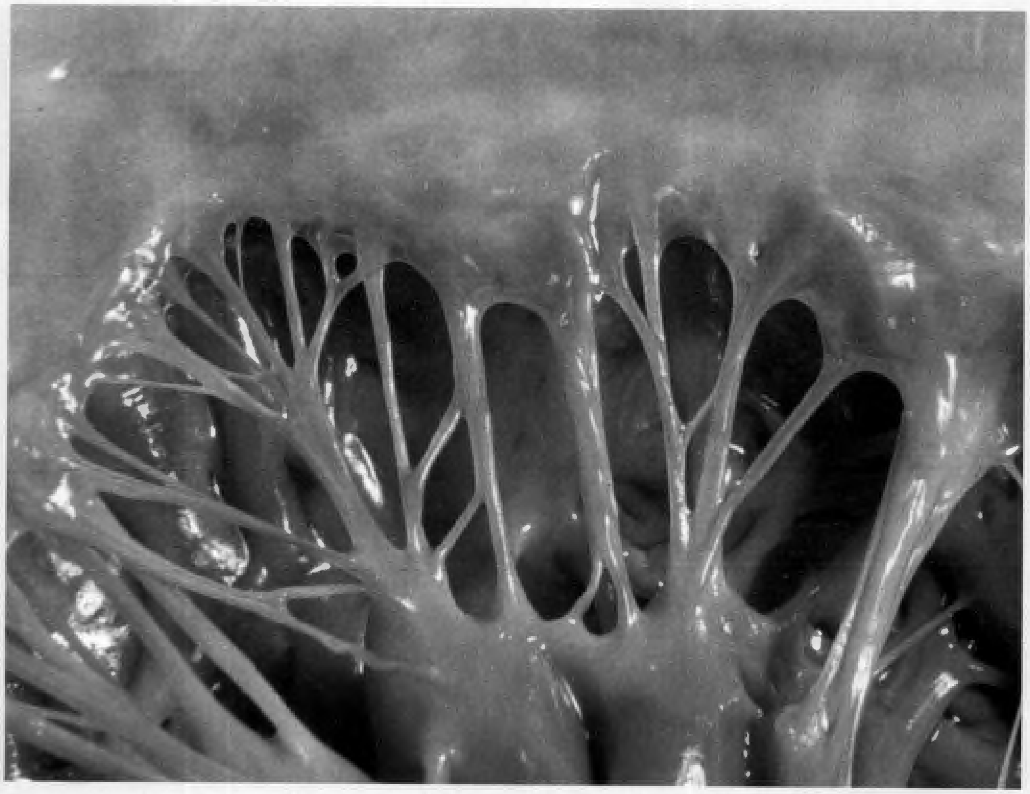


FIGURE 6. The junctional tissue at the postero-medial junctional zone of the normal mitral valve.

ring around the mitral orifice, or they are separated by small secondary cusps of irregular form and size ......" and to Gray's Anatomy[201], "Two small cusps are usually found in the angles between the larger cusps". Grant[203] (1948) refers briefly to a "short cuff" of tissue at these sites. These standard anatomical reference works fail to record the size or frequency of occurence of these additional cusps.

Rusted et al.,[209] (1952) consider it unusual for an accessory cusp to separate the two major cusps; an examination of 100 normal hearts revealed only 5 in which there was a tiny projection which conceivably could be called an accessory cusp. Harken et al.,[210] (1952) however stated that in 75% of 35 normal hearts studied, the mitral valve pattern was that of "4 triangular leaflets arranged circumferentially"; the 2 additional triangular projections were named the anterior and posterior "commissural leaflets". Chiechi et al[208] (1956) in an examination of 105 normal mitral valves found no accessory cusps in 41; in these valves the major leaflets were continuous with one another at their bases by means of the junctional tissue. Of the remaining 64 valves studied 22 had both anterior and posterior, 30 had only an anterior, and 12 only a posterior accessory cusp.

In the fresh healthy heart the cusps are white, glistening, tendinous, curtain-like flaps, which are perfectly smooth on the atrial surface, (Figs. 3,5.) but on the ventricular surface are ridged by the insertions of the chordae tendineae.(Figs. 2,7.) Nearly all the

The postero-lateral leaflet (ventricular, mural or lesser leaflet) (Fig. 5) is usually irregularly quadrangular with sloping apical sides.. Its length at the line of insertion (33 mms.) is only a few millimetres less than that of the aortic leaflet, while its height (14 mms.) is almost one half that of the aortic cusp. Its surface area is roughly equal to one-third the total valvular-tissue surface area (Chiechi et al.,[208] 1956).

The valvular tissue uniting these two cusps at their basal attachments and for a varying distance along their adjacent margins has been named the "junctional tissue". (Fig.6) It is frequently designated as a "valvular commissure", but the term is probably best used only when referring to a pathological heart in which the fusion of opposite cusps as a result of fibrosis has occured. The average depth of this junctional tissue measured from the free edge to the valve ring was found by Chiechi et al.,[208] (1956) to be 8 mms. at the anterior and 7 mms. at the posterior junctional region, and 8 mms. at both regions by Rusted et al.,[209] (1952).

The junctional tissue may become differentiated into one or two minor accessory cusps, which separate the aortic from the mural leaflet at each extremity. Considerable controversy exists however, regarding the incidence of occurence of these additional cusps. According to Cunninghams Textbook of Anatomy[202], "The bases of the (two mitral) cusps are continuous with each other at their attachment to the fibrous

FIGURE 7. Photograph showing insertion of chordae tendineae to the free edge and the periphery of the ventricular surface of the antero-medial mitral leaflet.

chordae which reach the aortic cusp however are attached near the free margin of this cusp, which therefore is smooth on both its surfaces. (Fig. 7) (Johnston and Whillis[201] 1954) The free margin of each cusp is irregularly dentated, the apices of the dentations being continued into the chordae tendineae. (Figs. 2, 5.) At these points and immediately above the margin, the cusps are considerably strengthened, but in the concave intervals between them, the margin is much thinner. (Fig. 2)

When viewed from the atrial aspect the cusps appear to be continuations of the atrial wall; (Figs. 3, 5.) when viewed from below they are separated from the ventricular wall by a peri-valvular space, which is interrupted, anteriorly and to the right, by the origin of the aorta. The walls of this space are ridged on the ventricular side by columnae carnea and on the valvular side by chordae tendineae, and it is crossed, near the base of the valve, by chordae of the third order. (Fig. 8)

Each cusp consists of a basic fibrous layer - the lamina fibrosa - which arises from, and is directly continuous with, the annulus fibrosus, and whose substance is reinforced by the chordae tendineae which are attached to it. This fibrous tissue is poorly nucleated, contains only few elastic elements, and its fibres lie for the most part parallel to the long axis of the valve cusp. Both the atrial and the ventricular endocardium are continued onto the corresponding surface of each cusp and become continuous with one another

FIGURE 8. The ventricular aspect of the postero-lateral mitral leaflet. The peri-valvular space, ridged on the ventricular side by columnae carneae and on the valvular side by second order chordae tendineae, and crossed near the base of the leaflet by chordae of the third order, is shown.

at the free edge of the cusp, the atrial layer being much the thicker of the two. Microscopically the endocardium consists of 3 layers (Quain[27] 1929):

(a) An endothelial layer - a single stratum of characteristic endothelial cells.

(b) The lamina propria - a strong connective tissue layer characterised in the atrium by a large amount of elastic tissue, arranged in a network of fine and coarse fibres. The ventricular endocardium contains but few elastic fibres. Between the lamina propria proper, and the endothelial layer, is a loose layer of delicate fibrillar tissue, sometimes described as a separate "subendothelial layer".

(c) A subendocardial layer of loose fibrous tissue most apparent on the atrial surface towards the base of the cusps and gradually disappearing as it is traced towards the free edge. Isolated bundles of muscle fibres, continuous above with the atrial musculature, run downwards in the long axis of the cusps in the subendocardial layer. These muscle fibres are best developed in the aortic leaflet, do not extend beyond the upper one-third of the cusp, and end below in pointed processes on the atrial surface of the lamina fibrosa.

The presence of blood-vessels in the atrio-ventricular valves is now generally accepted. Developmentally these enter the cusps from above with the atrial musculature, and from below along the muscular strands which become the chordae tendineae; as the valvular muscle regresses the vessels in large part disappear, and are afterwards confined in their distribution to the persisting muscle. It seems probable however that markedly vascular atrio-ventricular valves are not to be considered normal, but are the result of previous pathological change. (Kugel and Gross[211] 1926; Wearn et al.,[212] 1936; Koletsky[213] 1946.)

(iii) The Chordae Tendineae.

The chordae tendineae are rigid, glistening cords, which pass from each papillary muscle, fan-wise, to gain attachment to both major valve cusps and to the junctional tissue and/or to the accessory cusps inbetween, in such a way that the antero-lateral muscle and its tendons control the antero-lateral half of the valve, and the postero-medial muscle and its tendons control the corresponding postero-medial half. The chordae are of three orders according to Tandler[204] (1913):

I. Those which are inserted on the free edge of the cusps. They are numerous delicate threads, which arise from the other chordae near the cusp margin and often form a fine fibrous network before they are attached to it. (Fig. 2)

2. Those which are inserted at intervals on the ventricular surface of the cusp near its free edge, over which they pass to the attached border. (Fig. 2) They are distinctly thicker than the chordae of group I, 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. At their insertion most of these chordae spread out in a fibrous network, which is attached to the lamina fibrosa; some however pass through this network to be inserted into the annulus fibrosus at the base of this cusp.

3. Those which 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. These are short broad fibres which can be seen only when the other chordae are divided and the cusp is turned upwards. (Fig. 8)

Brock[200] (1952) has described the mitral orifice as consisting of a central horizontal and two lateral or receding oblique portions. At each extremity of the central portion are inserted those chordae that arise from the very summit of a papillary muscle and gain the most direct attachment to the valve cusps. These tendons, the areas of insertion of which have been termed the "critical areas of tendon insertion", are often thicker and stronger than those more obliquely placed tendons, which gain insertion principally into the lateral oblique portions of the valve cusps. Sokoloff et al.,[214] (1950), as a result of a study and survey of 200 hearts of all ages, had similarly shown in 1950, that the more centrally placed chordae of the anterior cusp are thickened and more powerful in every heart at all ages, when rheumatic infection can be excluded. Few oblique fibres pass medially to the horizontal portion of the valve leaflets, and this is especially so in the case of the antero-medial or aortic cusp. (Fig. 7) Chiechi et al.,[208] (1956) found a pattern similar to that described by Brock[200] (1952) in 71% of 105 normal antero-medial mitral valve cusps examined. An analagous pattern was found to be lacking on the ventricular leaflet.

Microscopically the chordae tendineae appear as round or oval cords, covered with a thin, closely adherent layer of endocardium which is continuous with that lining the papillary muscle below and the valve cusp above. Most of their substance is made up of relatively acellular collagen, this material being directed parallel to the long axis of the chordae. In hearts from subjects in the third decade or older, a subendocardial layer of collagen frequently encircles this central core. (Sokoloff et al.,[214] 1950)

(iv) <u>The Papillary Muscles.</u>

The papillary muscles belong to the system of columnae carneae of the ventricular musculature. Each is a conical muscular projection attached by its base directly to the wall of the ventricle at about the junction of its apical and middle thirds. Those of the left ventricle are typically 2 in number, and lie between the major mitral leaflets directly inferior to the valve junctional zones, one being antero-lateral, and the other postero-medial in position. Both muscles are situated in the lower inflow portion of the left ventricle, the antero-lateral one arising from the concavity of the antero-lateral wall of the ventricle and the postero-medial from the junction of the septal and posterior surfaces.

Both superficial and deep ventricular muscle fibres enter into the formation of the papillary muscles. The superficial bulbo-spiral fibres (Mall[215] 1911) which arise from the conus tendon, pulmonary root, trigonum fibrosum sinistrum, and the anterior,lateral,and posterior curvature of the left atrio-ventricular ring, and the superficial sino-spiral fibres (Mall[215] 1911) which arise around the tricuspid orifice, extend spirally downward towards the apex, form a vortex and penetrate to the interior of the ventricle. There they lie subendocardially, run spirally and attach to the fibrous atrio-ventricular rings. Some fibres however are pulled towards the interior of the ventricular cavity, those of the superficial bulbo-spiral muscle foriming a considerable portion of the posterior papillary muscle, those of the superficial sino-spiral muscle similarly entering into the formation of the anterior muscle. The deep muscle fibres of the ventricles are arranged in 3 layers. Each arises in the papillary muscles of one ventricle, and curving in an S-shaped manner turns in at the interventricular groove and ends in the papillary muscles of the opposite ventricle. (Johnston and Whillis[201] 1954)

Each papillary muscle may be single, double, triple or formed by more than 3 muscles, and a single muscle often contains a groove which leads in the direction of the junctional zone immediately above the apex of the muscle. (Fig. 5) Rusted et al.,[216] (1951) in a study of 200.normal hearts, reported that the antero-lateral muscle was usually single, but was grooved in more than 70% of the cases; at the postero-medial position there were 2 or 3 muscles (or a single muscle with 2 or 3 heads) (Figs. 2, 5) in more than 60% of the cases. Chiechi et al., (1956) found 83.8% of 105 normal hearts to have a single antero-lateral muscle and 70.5% to have multiple postero-medial muscles. The most frequent combination is a single antero-lateral and a double or triple postero-medial muscle. (Fig. 5)

From the apex of each muscle, (or group of muscles, in the event of a multiple muscle) arises a chordal "fan" which extends to the corresponding halves of both valve cusps and the junctional tissue or accessory leaflets inbetween. (Fig. 6)

Microscopically each papillary muscle is seen to be covered with a thin layer of endocardium, continuous at its base with that lining the general ventricular cavity and at its apex with that covering the chordae tendineae. This endocardial covering is thickest on the surface facing the "outflow portion" of the ventricle.

II. THE MECHANISM OF ACTION OF THE NORMAL MITRAL VALVE

Anatomically the mitral valvular mechanism comprises 4 main structures, and as is to be expected, each plays a part during the normal opening and closing of the valve. Basically the valve orifice is guarded by the cusps, which constitute a "flap-type" valve, activated by differential hydrostatic pressures and restrained by their anchoring chordae tendineae and papillary muscles. The details of the mechanism of normal valve action have however not been established with certainty, and contreversy still exists concerning the exact role of the various valvular components.

Closure of the mitral valve.

That a difference between the intra-atrial and intra-ventricular hydrostatic pressure is a major factor in the activation of the normal valve cusps is undoubted. In a study of the normal mitral valve in perfused animal hearts Smith et al.,[217] (1950) noted that the mitral cusps closed only if fluid was present in the ventricles. A similar observation was made by Kantrowitz et al.,[218] (1951) during experimental left-heart by-pass, and our own observations during open left-atriotomy, using total cardio-pulmonary by-pass, have confirmed the accuracy of these reports.

At the onset of ventricular systole the atrio-ventricular valve cusps are probably already in apposition (Guyton[219] 1956). On the basis of in vitro and perfusion experiments, Henderson and Johnson[220] (1912) held that sudden stoppage of ventricular inflow at the end of atrial systole causes a zone of negative pressure in the area of the valve cusps. Influx of blood into this area from the sides of the vantricle would cause the cusps to roll closed before the onset of ventricular contraction. Wiggers[221] (1923) however pointed out that atrial injection does not stop suddenly, but rather there is a gradual cessation of flow as atrial systole ends. Krehl[222] (1891) and Straub[223] (1911) have attributed this valve closure to eddy currents set up behind the open valve leaflets as blood flows into the ventricle, and Rushmer et al.,[224] (1956) consider that increased chordal tension during ventricular diastolic distension draws the cusps nearer to one another.

According to Little[225] (1951), pre-systolic cusp apposition is due to back-flow from the ventricle to the atrium following atrial systole. In animal experiments, Little has shown that a small pre-systolic increase in ventricular pressure occurs as the result of atrial systole. Contraction of the atrium results in a forward flow of blood into the ventricle, and also a retrograde flow into the entering pulmonary veins; atrial pressure rises to a peak and then falls. The intra-atrial pressure drop allows the intra-ventricular pressure to exceed that within the atrium; back-flow from the ventricle to the atrium occurs, and the atrio-ventricular valve leaflets close even before the onset of ventricular systole. Such pre-systolic cusp apposition must serve to increase the efficiency of ventricular contraction, as no blood can then be regurgitated into the atrium at the onset of ventricular systole.

During the isometric contraction phase of the cardiac cycle, the ventricular muscle contracts and the intra-ventricular pressure rises steeply; the atrio-ventricular valves are closed and bulge in a dome-shaped manner into the cavity of the atrium. The intra-ventricular pressure is still lower than the aortic diastolic pressure, so no blood can leave the ventricle; the tension in the ventricle is rising but its volume remains constant and no shortening of muscle occurs. Intra-ventricular pressure exceeds the aortic pressure, the semi-lunar valve opens, rapid ejection of blood into the aorta occurs, the ventricular muscle shortens and the ventricular volume rapidly diminishes.

All parts of the ventricle do not contract simultaneously. During the latter part of systole some portions of the ventricular myocardium cease to contract, and as fewer units are functioning the pressure within the ventricle begins to decline slowly, and systolic discharge lessens. Ventricular diastole then sets in and the intra-ventricular pressure drops sharply. A backward flow of blood towards the heart occurs in the aorta and is halted by the closure of the aortic valve. Intra-ventricular pressure continues to fall sharply as the muscle relaxes, but ventricular volume remains constant and the atrio-ventricular valve remains closed due to the fact that intra-ventricular pressure still exceeds that within the atrium

Normal valve closure is equally dependent upon the chordae tendineae and papillary muscles, which act, in part, as passive anchoring stays, to prevent "flapping" or eversion of the cusps into the atrium during ventricular systole; those attached to the antero-medial cusp also prevent its billowing into the aortic outflow tract. In addition however, the papillary muscles are able to actively contract, and it would appear that they, indirectly attached to the cusps via the chordae, must exert some active influence during cusp action.

Kantrowitz et al.,[218] (1951) have shown by cinematic studies of the action of the exposed mitral valve in the experimental animal, that coincident with the shortening of the apex to ring distance which occurs during systole, the chordae appear to slacken. This observation is possibly an artefact (Bailey[226] 1955) as the studies were performed on an empty heart, and is not in accordance with that of Rushmer et al.,[224] (1956) who consider on the basis of their experiments using cineflurography, that the papillary muscles contract early in systole with resultant tautening of the chordae. Physiological evidence (Best and Taylor[227] 1955) that the cardiac impulse arrives early in the region of the papillary muscles lends support to this contention.

According to van der Spuy[206] (1958), papillary muscle contraction early in systole has the added effect of pulling the aortic leaflet posteriorly, and actually plays a part in the initiation of cusp movement during systole. Such an action presupposes that cusp apposition occurs only after the onset of ventricular systole, and is not in agreement with the views of Henderson and Johnson[220] (1912), Little[225] (1951), and Guyton[219] (1956) already cited.

The importance of the chordae and papillary muscles for satisfactory valve closure is readily demonstrated experimentally. Should either of these structures be intentionally severed during open left atriotomy, or in hearts set up in the artificial pulse-duplicator to be described, cusp apposition during systole is imperfect, and flapping or eversion of the leaflet occurs. (Fig. 9) In addition, numerous cases of deranged mitral valve action, the result of rupture of the chordae tendineae (Bailey[226] 1955) or a papillary muscle, (Brock[81] 1950) have been recorded.

A third mechanism which plays a part in the closure of the normal mitral valve is contraction of the valve ring during ventricular systole. Such an action was demonstrated by Smith et al.,[217] (1950) who cut the valve ring in the excised perfused beating heart and were able to observe definite shortening and lengthening with each cardiac cycle. Kantrowitz et al.,[218] (1951) noted a sphincter-like action of the valve ring during experimental open heart operations, and Brock[200] (1952) confirmed this observation clinically by palpation during closed left-heart operations.

The result of such annular contraction is to decrease the orificial area of the valve during systole. In addition as van der Spuy[206] (1958) has pointed out, the origin of the root of the aorta indents the antero-medial portion of the valve ring. During systole therefore, systolic expansion of the aorta causes flattening of the valve ring. The significance of this action is best appreciated if we compare

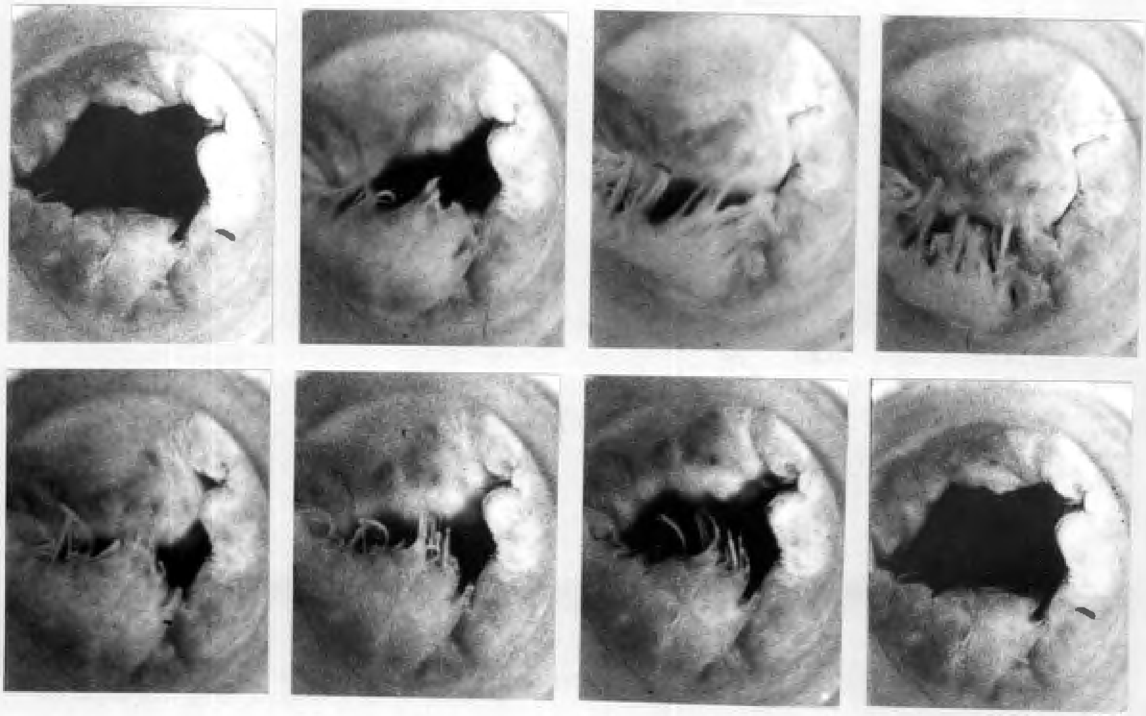


FIGURE 9. Cycle of movements of mitral valve with severed chordae tendineae, showing closure and subsequent opening.

the mitral valve to an inverted cone, the base of which is represented by the valve ring. Compression of any cone in an antero-posterior plane will result in its anterior and posterior sloping walls becoming approximated to one another. Compression of the valve ring therefore, has the effect of approximating the aortic and mural leaflets and the area of cusp apposition for a given degree of cusp excursion is increased.

In order to study and photograph the action of the valve, normal human hearts removed at autopsy were set up in an artificial pulse duplicator to be described. Care was taken to ensure that the anatomy of the parts was not disturbed and intra-cavitary pressures and heart rate were adjusted to conform with those in the normal human circulation. The action of the valve ring, and the papillary muscles could not of course be imitated, and the injection of fluid via the ventricular apex, in order to simulate the sudden rise in intra-ventricular pressure, possibly caused a "jet" effect which does not occur in the heart normally. Also, ventricular distension during simulated systole, as opposed to contraction during normal systole, must alter chordal tensions. Nevertheless, the "flapping" action of the valve leaflets could be photographed and studied, (Fig. 10) and appeared to simulate closely the appearances seen during direct vision operations on the mitral valve of experimental animals.

A study of slow-motion cine photographs of a valve set up in the pulse duplicator shows that during simulated systole, the anterior

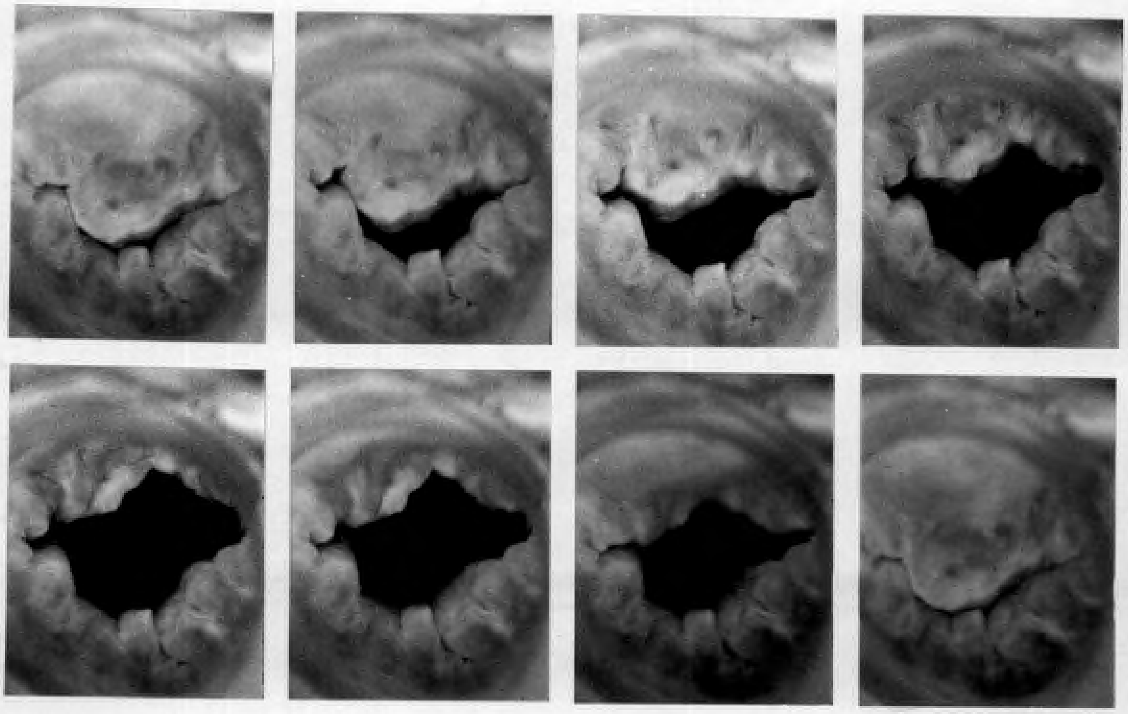


FIGURE 10. Cycle of normal mitral valve movements showing the opening and subsequent closure.

and posterior leaflets become apposed to one another along their apical and commissural margins, and as previously observed by Davila et al.,[228] (1956), the anterior cusp undergoes a much greater excursion than the posterior (Fig. 10). Rushmer et al.,[224] (1956) have shown by radiographic studies of normal valves tagged with radio-opaque markers, that cusp excursion is greater in the heart exposed during thoracotomy than under normal conditions. These authors suggested that a decrease in cardiac size, as a result of the loss of a negative intrathoracic pressure during the former procedures, alters normal chordal tensions, thus permitting excessive cusp excursion. Any such pressure changes however, while possibly allowing of greater freedom of cusp movement, should not alter the observed mechanism of leaflet action.

As systole progresses and the intra-ventricular pressure rises, a progressive increase in the area of cusp contact occurs. The antero-medial cusp billows prominently upwards and backwards, the postero-lateral slightly upwards; the valve leaflets become more tightly approximated, and in addition mutually support one another.

An entirely different machanism of valve function was suggested by Lutembacher[229] (1950), who described valve closure as a "bunching up", in which the cusps, the chordae, and the papillary muscles come together in such a way that the closure of the orifice is aided and secured by an actual interlocking of these structures. This concept was however based on a study of autopsy specimens, and direct vision observation during open-heart operations has not confirmed such an action. In addition, the alternative mechanism of closure suggested by Brock[200] (1952), that the orifice is occluded entirely by the aortic cusp forcing the much smaller mural cusp against the posterior wall of the ventricle has not been observed by us, either in studies using the pulse-duplicator or during experimental and clinical open left-heart operations.

The line of contact of the valve leaflets during systole has the appearance of an irregular slit concave forwards, whose postero-medial and antero-lateral extremities do not extend to the valve ring, and which is situated much nearer to the posterior than the anterior portion of the mitral annulus. The antero-medial leaflet thus occludes a greater area of the valve orifice than does the postero-lateral, (Fig. 10), which occupies a subsidiary or adjuvant function in sealing a narrow posterior crescent of the orifice.

The significance of the lateral "junctional zones" or "accessory cusps" has received little attention from previous observers - their very existance has been ignored by many. Our own experiments have demonstrated that during systole these areas bulge towards the atrium in a similar manner but to a lesser degree than do the anterior and posterior cusps. In addition to providing leaflet tissue for orifice occlusion, they appear to play an important role as supports for the lateral portions of each major cusp. That their integrity is essential for valve competence is easily demonstrated experimentally by disrupting the continuity of these areas outwards to the mitral ring; regurgitation through the incised areas immediately occurs. Similar observations have been recorded by Bailey[226] (1955) following the accidental division of these areas during mitral commissurotomy on patients suffering from mitral stenosis.

In an attempt to study the action of the valve leaflets in slow motion in the heart in situ, experimental animals were subjected to open left atriotomy and ventricular fibrillation was induced, (McKenzie and Barnard[230] 1960). The ventricular blood was then aspirated and slowly allowed to re-accumulate. As the intra-ventricular blood volume increased, with resultant rise in intra-ventricular pressure, it could be seen that the major cusps and the accessory cusps or junctional zones billowed towards the atrium and that the area of cusp apposition increased as described. The limitations of such observations are however similar to those when using the pulse duplicator.

Opening of the mitral valve.

Opening of the mitral valve at the end of ventricular systole appears to be largely dependent upon a pressure differential between the atrium and ventricle. At the end of the isometric relaxation phase of the cardiac cycle, atrial pressure, which has been rising throughout the greater part of ventricular systole, exceeds the intra-ventricular pressure. The atrio-ventricular leaflet floats open because of the pressure difference between the two chambers, and rapid inflow of blood into the ventricle occurs. Approximately 60% of the total ventricular filling takes place in this way and the absence of atrial systole has little influence on ventricular filling. Little[225] (1951) has shown however that in the absence of atrial systole the valve cusps are unlikely to be in apposition before the succeeding ventricular contraction, with the result that regurgitation occurs during the early part of the latter phase.

Just as during systole the annulus contracts, so during diastole it relaxes; the size of the valve orifice is therefore increased. According to Brock[200] (1952) this is of little moment in valve function, as the valve consists of a central horizontal and two lateral receeding portions, the central portion alone representing the effective valve orifice, the aperture between the lateral receeding portions being blocked by chordae proceeding to the relevant papillary muscles. Relaxation of the mitral ring during diastole however has the additional effect of decreasing the flattening of the valve "cone", with a resultant decrease in the area of cusp contact.

The function of the papillary muscles and chordae tendineae during diastole is disputed. According to Brock[200] (1952) the muscles relax and the chordae are lax. Kantrowitz et al.,[218] (1951) however maintain that the chordae remain taut during diastole, thus actively retracting the valve leaflets. Rushmer et al.,[224] (1956) on the other hand believe that increased tension of the chordae, due to ventricular distension during diastole and especially following on atrial systole, draws the cusps nearer to one another.

In the course of experimental open left-heart operations we have repeatedly observed that the mitral leaflets flap apart during diastole, despite the absence of blood within the left heart chambers. The factors responsible for this action have not been ascertained with certainty, but it would appear to be due to an active retraction of the cusps by the chordae as described by Kantrowitz et al.,[218] (1951). This observation does however demonstrate that some factor or factors other than a hydrostatic pressure difference plays a part during the opening of the normal valve.

III. THE MECHANISM OF PRODUCTION OF MITRAL INSUFFICIENCY.

The competence of the normal mitral valve is dependent upon occlusion of the atrio-ventricular orifice by the valve leaflets during ventricular systole. The leaflets however are but one component of a complex whole, consisting of four parts, the mitral annulus, the valve leaflets, the chordae tendineae, and the papillary muscles, the integrity of all of which are essential for normal mitral function.

Insufficiency of the valve is due to the inability of the leaflets to co-apt and occlude the atrio-ventricular orifice during ventricular systole, and may be the result of an abnormality of any one or more of the four components of the valve mechanism. Thus

(i) an absolute loss of leaflet substance due to a defect or perforation, or scarring and shortening of the cusps,

or (ii) an effective loss of leaflet substance due to a shortening of the musculo-tendinous control, with resultant decreased cusp mobility, or rupture of the musculo-tendinous mechanism with a resultant "flail" action of the detached portion of the leaflet,

or (iii) a relative loss of leaflet substance due to dilatation of the mitral annulus, either alone, or in combination, may be the essential structural abnormality causing the valve to be incompetent.

The pathological states which may bring about such defective valve function may be classified as congenital, traumatic, inflammatory, or functional in origin.

Congenital Mitral Insufficiency.

Mitral regurgitation due to a congenitally cleft mitral septal leaflet associated with an ostium primum defect or persistent atrio-ventricular canal (Fig. 11) is a not uncommon lesion, and in our first 30 open-heart operations we have encountered this defect on two occasions. (Barnard, McKenzie et al.,[138] 1959).

Congenital mitral regurgitation not associated with such defects is however extremely rare. Two cases have recently been reported by Starkey[231] (1959) in which the regurgitation was due to congenital enlargement of the mitral annulus and Bailey et al.,[123] (1954) recorded 3 cases with one or more congenital perforation of one or both valve leaflets which permitted regurgitation of blood even though the natural valve orifice was capable of complete closure by marginal contact. A similar case has been encountered by us at autopsy (Fig. 12).

In some hearts without other malformations, but in the experience of Edwards and Burchell[232] (1958), more commonly in association with ventricular septal defect, there is anomalous insertion of some of the chordae, usually of those connecting with the posterior leaflet. The anomalously inserting chordae are usually unduly short, their lower ends attach more basally than normal, and they are associated with accessory commissures (or clefts) in the posterior leaflet. These chordae

FIGURE 11 a. Congenital cleft of the antero-medial mitral leaflet. (seen from the left ventricle)

FIGURE 11 b. Congenital cleft of the antero-medial mitral leaflet. (seen from the left atrium)

FIGURE 12. Congenital perforation of the antero-medial mitral leaflet, seen from the ventricular aspect.

appear to exert a restraining influence on the leaflet and prevent proper excursion for closure at the accessory commissure.

Traumatic Mitral Insufficiency

Mitral insufficiency is a rare complication of trauma and may be caused by indirect or direct violence. A valvular lesion, the result of indirect violence is most likely to be a rupture of the chordae tendineae (Barber[233] 1944). Horton- Smith[234] in 1902, described such an accident in a healthy workman, who died 3 months later of congestive cardiac failure, and Frothingham and Hass,[235] (1934) and Kissane and Koons[236] (1938) have reported similar cases.

Mitral insufficiency may also result from direct violence. The unique case of a young man who sustained a bullet wound of the septal leaflet, and died several years later of heart failure from the resulting incompetence, was reported by Adam [237] in 1927, Traumatic rupture of the antero-lateral papillary muscle with resultant regurgitation has been described by Glendy and White[238] (1936), whose patient died 26 hours later, and rupture of the anterior mitral cusp by Berblinger[239] (1910). Anderson[240] (1940) and Cameron[241] (1942) have reported cases of clinical mitral insufficiency following direct trauma to the thorax; although the abnormal physical signs persisted, both patients recovered, so the exact anatomical diagnosis was not confirmed.

Now that surgery for mitral stenosis has become a frequent undertaking, a much more common type of traumatic mitral insufficiency is the inadvertent creation of regurgitation during attempts at surgical mobilisation of the fused valve cusps. This complication occured in 24.8% of 635 consecutive operations for pure mitral stenosis, and in 26.7% of 176 consecutive operations for mitral stenosis associated with insignificant regurgitation, performed by Bailey et al.,[123] (1954), who stated however that in only a small percentage of these was the traumatically induced lesion of any clinical significance.

Such insufficiency may result from;

(i) Extension of the commissurotomy beyond the normal orificial limits, and hence beyond the limits of tendinous support.

(ii) Division of the mitral annulus, by extension of the commissurotomy into the heart wall, with resultant dilatation of the annulus.

(iii) Deviation of the line of valvular separation from the natural anatomical line of the valve orifice, with consequent deprivation of one leaflet of its normal chordo-papillary support.

(iv) Actual division of the continuity of one of the valve leaflets, the severity of the resultant regurgitation depending upon the extent of the division and which leaflet has been damaged. Complete division of the septal leaflet usually proves fatal within minutes, a comparable lesion of the mural cusp being less serious but nevertheless haemo-dynamically significant (Bailey et al.,[123] 1954).

(v) Avulsion of a papillary muscle (Brock[81] 1950) from its ventricular origin, or division of chordae tendineae (Fig.9) (Bailey[226] 1955).

Mitral Insufficiency of Inflammatory Origin.

(i) Rheumatic Endocarditis.

Insufficiency of the mitral valve is most commonly the result of deformity of the valve mechanism, secondary to previous rheumatic involvment. The basic valvular lesion, although almost universally termed an endocarditis, is an inflammation of the valve proper - a valvulitis - with secondary involvment of the endocardial surfaces (Shaw[242] 1929).

In the acute stages of rheumatic inflammation the valve leaflets are slightly thickened due to oedema, and show tiny translucent nodules (verrucae) which vary in size from less than one millimetre to 3 mms., and which are located along the lines of contact on the atrial aspect of the mitral cusps. The nodules are firm and not easily detached, may be arranged singly in a row or in clusters of 2 or 3, occasionally are fused forming a pyramidal ridge along the line of closure, and may be present on the chordae and rarely on the papillary muscles. Histologically, the valve cusps, the valve ring (Gross and Friedberg[243] 1936), and the chordae (Boyd[244] 1947), show evidence of an inflammatory response, and in the region immediately adjacent to the vegetations there is a marked fibroblastic proliferation.

As the acute inflammation subsides secondary fibrosis occurs, and with each repeated attack of rheumatic inflammation (should more than one attack occur) the gross alteration of the valve tends to become more pronounced. The valves become thickened, shortened, and more rigid (Figs. 13, 14, 15.), gross vascularisation and irregularity of the surface is usually present, and calcification may occur. The chordae become thickened and shortened, and incorporated into the valve cusps (Fig. 15) (Tweedy[245] 1956) and the papillary muscles become approximated to the cusp margins (Fig. 14). In addition, fusion of the chordae to one another may occur, and occasionally they may rupture or become detached from the cusp margins (Bridgen and Leatham[246] 1953). Histologically the increased thickness is due to an increase in fibrous and elastic tissue throughout the valve leaflet and ring. Inflammatory cells tend to disappear and the fibrous tissue is more homogenous and hyaline in appearance. Capillaries and thick walled vessels are present, being more numerous in the superficial layers of the valve. Calcification is common and the lime salts may be distributed diffusely or in the form of large nodular masses.

The deformity of the valve mechanism resulting from the healing processes described, may result in mitral insufficiency as follows;

(i) Thickening and shortening of the cusps results in an absolute loss of leaflet substance (Fig. 13); during ventricular systole therefore, the leaflets may be unable to approximate and occlude the valve orifice.

(ii) Rigidity of the cusps with consequent decreased mobility, may prevent systolic apposition of the cusps, and irregularity of their margins may prevent accurate systolic apposition (Fig. 13).

FIGURE 13. Rheumatic mitral incompetence - the abnormal valve seen from the left atrium. Note the thickened, shortened, rigid cusps with irregular margins. The postero-lateral leaflet (on the right) is maximally involved.

FIGURE 14. Rheumatic mitral incompetence - abnormal valve showing characteristic shortening and thickening of the cusps and chordae, and approximation of the papillary muscle to the cusp margins. The postero-lateral leaflet (on the right) is maximally involved.

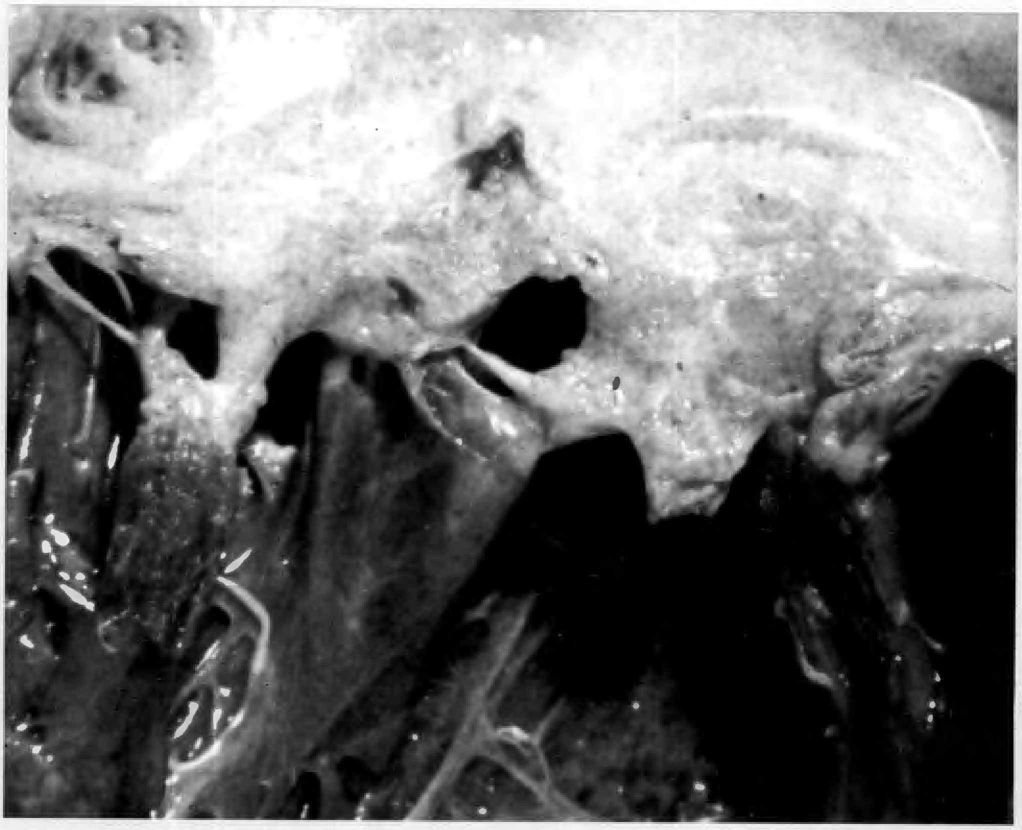


FIGURE 15. Rheumatic mitral incompetence - photograph of valve showing gross thickening, shortening and calcification of the cusps. In addition, the chordae are thickened, shortened and incorporated into the valve cusps, and the papillary muscles are approximated to the cusp margins.

(iii) Shortening of the chordae tendineae (Figs. 14, 15.) or adhesions between the mural cusp and the ventricular myocardium may limit cusp mobility and hence prevent systolic apposition of the cusps.

(iv) Shortening of the chordal supports of one leaflet may result in the two cusps coming to lie at different levels between the atrium and ventricle during systole, occlusion of the orifice therefore being incomplete.

(v) Rupture or detachment of chordae tendineae may result in a "flail" action of a cusp or portion of a cusp. (Fig. 9)

(vi) Dilatation of the mitral annulus results in a relative deficiency of leaflet substance with resultant inability of the latter to occlude the valve orifice during systole.

Pure mitral regurgitation of rheumatic origin is however extremely rare, and pathologically, stenosis and regurgitation are almost invariably co-existant (White[247] 1951; Hall[248] 1953; Gould[249] 1953). In practice therefore, as Brock[200] (1952) basing his conclusions on incompetence observed directly at operation has pointed out, mitral insufficiency is observed in one of 3 forms;

(i) A small regurgitant jet occuring from a small grossly stenosed orifice, the margins of which are fibrous or supported by calcium so as to be quite rigid and unable to approximate during systole. As the stenosis in such a case is so severe as to permit very little blood to enter the ventricle, it can scarcely allow a significantly greater amount to regurgitate.

(ii) A moderately powerful regurgitant stream, occuring from a narrowed but not grossly stenosed orifice. Examination of such a valve shows thickened, rigid, often calcified cusps with limited mobility. The chordae are thickened, shortened, and fused, and the dense fibrosus extends down to involve the papillary muscles. The main process in such a case appears to be a peripheral fibrous contracture with resultant holding open of the central pathway of the fused shortened cusps. The magnitude of the regurgitant jet varies greatly and may be considered in many cases to be inversely proportional to the amount of co-existing stenosis.

(iii) A powerful regurgitant jet, occuring from a large orifice at least 3 - 4 cms. in diameter. In this lesion there is no stenosis. The cusps are fibrous and shortened and the valve ring circumference is larger than normal, probably from secondary dilatation. According to Wood[250] (1952) dilatation of the mitral annulus is a rare cause of incompetence in chronic rheumatic heart disease; Bridgen and Leatham[246] (1953) however at autopsy examination of 9 cases of rheumatic mitral incompetence, found 8 to have a dilated valve ring.

Bailey et al.,[123] (1954), Harken et al.,[134] (1955), and Nichols[178] (1957) have observed that regurgitation is predominant at, and usually limited to the posterior portion of the valve orifice. This has been attributed to the anatomical difference between the anterior and posterior portions of the valve. There is characteristically a relatively greater abundance of intrinsic valvular tissue anteriorly than posteriorly, especially in the junctionally zone regions, and hence a significantly greater degree of overlap of the leaflets during valve closure, in the anterior than the posterior region. Should symmetrical shortening of the valve leaflets in all portions of the valve orifice occur, the existing excess valvular tissue will be reduced symmetrically, until it becomes impossible for the shortened leaflets to become apposed in all portions of the aperture. Since there is less excess or "reserve" valvular tissue posteriorly, this type of regurgitation will appear first in the region of the posterior junctional zone.

Paravisini et al.,[251] (1953), observing that the anterior junctional zone lies relatively close to the ventricular wall, while the posterior lies somewhat closer to the centre of the atrio-ventricular passage, have postulated that the mural leaflet is short and of little importance in maintaining valve competence anteriorly, while it is of great importance posteriorly. These authors have also postulated that the rheumatic process has a selectively destructive effect upon the mural leaflet, and Johnson's[197] (1956) observation that 70 of 100 rheumatic hearts examined at autopsy showed maximal involvement of the mural cusp, is in accordance with this view. Reasoning from these two premises it may be expected that the localisation of valvular incompetence will usually be located at the posterior portion of the orifice.

(ii) Non-rheumatic Endocarditis.

The present tendency to consider all valvular deformities encountered either in the clinic or at autopsy, as rheumatic in origin, in spite of insufficient evidence to satisfactorily identify the aetiological agent, may well be questioned. It does not seem that enough is known concerning the valvular damage in a wide variety of toxic, infectious and metabolic processes to dismiss all aetiologic possibilities except rheumatic fever in the interpretation of any valvular deformity.

It is possible that not all valvular lesions are rheumatic in origin (White[247] 1951) and in this connection such studies as those of Csirer[252] (1913) and de Vecchi[253] (1931) may be noted. These investigators found histiological evidence of acute valvulitis in children in the presence of such diverse diseases as scarlet fever, diphtheria, broncho-pneumonia, meningitis and tuberculosis without gross evidence of valvular damage. From these studies it seems possible that patients, especially children, who survive such infectious processes, also have acute valvulitis, which in some instances may heal with resultant valvular deformity.

The possible role of healing of acute bacterial endocarditis in the genesis of cardiac valvular deformities has been discussed by Saphir[254, 255] (1941, 1942) and Moore[256] (1946). In this disease, which may be caused by a wide variety of organisms (Thayer[257] 1931), the valve cusps, and frequently the chordae, are the site of deposition of vegetations, which consist of fibrin, leucocytes, and colonies of bacteria. Ulceration of the cusp endocardium is common and perforation of a cusp (Degowin et al.,[258] 1945) or rupture of chordae may occur. With recovery scarring undoubtedly occurs, and could conceivably bring about insufficiency of the valve in the same manner as does rheumatic endocarditis, but whether or not such scarring is responsible for some cases of mitral valvular disease is uncertain (White[247] 1951).

Similarly, sub-acute bacterial endocarditis may be responsible for deformity of the heart valves. Pathologically the lesions are proliferative rather than destructive, but occasionally large portions of a cusp may be destroyed. Characteristically large friable polypoid vegetations originate along the line of contact of the cusps and may spread to cover the cusp and involve the chordae, which may be weakened and rupture (Hall[248] 1953; Edwards and Burchell[232] 1958). Microscopically the vegetations appear as amorphous masses of fused platelets and fibrin showing masses of bacteria on their surfaces. The valve is infiltrated with mononuclear cells, polymorphonuclear cells are conspicuously absent, and there is a distinct tendency to repair, as is shown by fibroblasts in the deeper parts of the lesion.

It has been stated that an active or healed rheumatic lesion is present in from 75% (Gross and Fried[259] 1937) to 90% (Clawson[260] 1940) of cases of sub-acute bacterial endocarditis. Healing may therefore increase the extent of valvular deformity, but most of the deformity is usually the result of the previous rheumatic involvement (White[247] 1951).

(iii) Syphilitic Endocarditis.

There are only 2 extremely rare possibilities for syphilitic involvement of the mitral cusps. Either gummata may be present in the valve or the adjoining myocardium, with secondary extension into a leaflet or the syphilitic process may extend from the base of the aortic valve downwards to the aortic leaflet of the mitral valve.

Staemmler[261] (1930) reported one patient, and Blackman[262](1935) reported 2patients, in whom signs consistent with a diagnosis of mitral incompetence had been present during life, and in whom, at autopsy syphilitic changes in the aortic leaflet of the mitral valve, continuous with similar lesions at the root of the aorta and the aortic valve were demonstrated. Grossly the lesions consisted of a diffuse leathery thickening of these areas and microscopically, gummatous necrosis or dense valvular scars, with peri-vascular round-cell infiltration were found.

Spaulding and von Glaun[263] (1921) reported a case of rupture of the posterior papillary muscle of the left ventricle due to syphilis. The patient died suddenly during a recurrent episode of congestive cardiac failure, and microscopic examination of the stump of the ruptured muscle revealed a central focus of coagulative necrosis surrounded by a thin sub-endocardial zone of fibrosis in whic a Levaditi preparation revealed spirochaetes.

Such instances are however extremely rare, so rare in fact that it may well be stated that syphilis practically never involves the mitral valve (Gould[249] 1953), and as eminent an authority as Boyd[244] (1947) has stated that "syphilis attacks only the aortic valve, never the mitral".

Functional Mitral Insufficiency.

It is generally recognised that a lack of myocardial tone may result in dilatation of the mitral annulus fibrosus. Hence even a valve with normal leaflet structure becomes unable to hold back the regurgitant stream, because of the increased size of the atrio-ventricular orifice.

Such annular dilatation may occur during toxic states, in the course of acute infections and in certain types of cardiac failure due to loss of myocardial tonicity, and in many cases, apparently, is transient, disappearing on recovery from the initiating toxemia or congestive failure. A less reversible type of functional insufficiency may occur in patients with massive left ventricular enlargement, due to hypertension, aortic stenosis, or aortic regurgitation, the essential defect, as before, being a dilatation of the atrio-ventricular ring.

It appears that once annular dilatation has progressed to, or beyond, a certain critical point, a vicious circle becomes established. With each ventricular systole a regurgitant jet is propelled into the left atrium, which responds by dilatation and hypertrophy. Simultaneously the left ventricle, labouring to maintain an adequate systemic output under impaired hydraulic conditions, is overworked. It too, responds by undergoing dilatation and hypertrophy. As the atrium and ventricle enlarge, the common point of their continuity - the atrio-ventricular ring - does likewise. Existing insufficiency is thus aggravated, and in turn determines further compensatory myocardial dilatation and hypertrophy, which leads again to further annular dilatation and so on.

According to White[247] (1951) and Edwards[264] (1958), downward displacement of the papillary muscles as the result of left ventricular dilatation may also cause functional mitral insufficiency. The chordae tendineae are of limited length, and with their attachments to the papillary muscles moved away from the base of the heart, their insertions on the valve cusps are likewise displaced downwards. This results in an inability of the cusps to close tightly, no matter how tautly the chordae may stretch or how elastic the cusps may be.

It is probable that such mechanisms are active, to some degree, in every case of mitral insufficiency. The concept therefore, is not merely that the left ventricular myocardium fails from mitral insufficiency of stationary amount and degree, but rather is faced with an ever increasing load due to a gradual but constant enlargement of the mitral orifice (Glover and Davila[170] 1957).

IV. THE HAEMODYNAMIC AND SECONDARY PATHOLOGICAL EFFECTS OF MITRAL INSUFFICIENCY.

Since both stenosis and regurgitation are generally combined to a greater or lesser degree in cases of organic mitral disease, the effects on the heart depend in part on the relative amounts of stenosis and regurgitation, and in part on the absolute degree of the valvular disease.

In pure mitral insufficiency, blood regurgitates into the left atrium during ventricular systole, thus decreasing the systolic discharge into the aorta and increasing both the volume of the left atrium and the pressure within it.. Wiggers[265] (1952) has shown that the rise in left atrial volume and pressure, which is determined by the amount of regurgitation, is slight during the period of isometric contraction, maximal during the period of systolic ejection, and that it continues to rise at a decreased rate during the period of isometric relaxation. Physical factors alone account for such a time course of regurgitation. As isometric contraction is of short duration (.05 secs.) and the pressure increase approximately 70 mms. Hg., the inertia of blood within the ventricle cannot be rapidly overcome; any considerable reflux is dynamically impossible even when an orifice of large size exists. The systolic ejection phase however lasts from .15 to .25 seconds and the intraventricular pressure ranges from 70 to 160 mms. Hg. The maintenance of such pressures over a longer time interval determines the considerable backflow during this phase. Finally intraventricular pressure exceeds the intra-atrial during the period of isometric relaxation, which lasts for about .08 seconds. Regurgitation therefore continues despite the fact that early diastole is in progress.

When the left ventricle relaxes in diastole, it is subjected to the increased filling pressure built up in the atrium during systole, and since there is no obstruction at the mitral orifice, it fills rapidly and dilates to accomodate the extra blood that leaked back during the previous cycle. The stroke volume of the left ventricle is therefore increased (Starling's Law[266]) by the amount of regurgitant blood, forward flow is maintained as near to normal as possible, and the left ventricle as a result of the increased work which it has to perform, undergoes hypertrophy. Dilatation of the mitral ring and displacement of the papillary muscles secondary to dilatation and hypertrophy of the chambers of the left heart may also occur, with addition of an element of "functional insufficiency" and establishment of a vicious circle mechanism.

Although the left atrial pressure may be very high during ventricular systole, it falls quickly to ventricular level during diastole, so that mean atrial and pulmonary artery pressures are lower than in mitral stenosis of comparable severity. Such passive pulmonary hypertension in mitral insufficiency is rarely high enough to excite a vasoconstrictor response, so pulmonary vascular resistance although showing a moderate rise in severe cases, rarely reaches extreme levels (Wood[250] 1956).

Right ventricular hypertrophy therefore tends to be less conspicuous than in mitral stenosis, but hypertrophy and dilatation of both right heart chambers may occur in the later stages of the disease (White[247] 1951).

In many cases of mitral valve disease evidence of active or healed myocarditis or serious coronary artery disease may be present. In others the myocardium may be normal except for hypertrophy, and in the later stages may become exhausted and fail without evidence of pathological change. Thus it is frequently the valvular lesion and not the myocardial disease that eventually causes failure and death (Gould[249] 1953), although it is equally true that active infection or some other complication may prove too great a burden for the heart that is already overloaded.

The pulmonary changes consequent on these haemodynamic disturbances consist of congestion with dilatation of the pulmonary arterioles and capillaries, and thickening of the vessel walls, interstitial tissue, and alveolar basement membrane (Becker et al.,[267] 1951). Systemic effects include changes characteristic of congestive failure. According to Wood[250] (1956), the right ventricle may very well not be overloaded, and he attributes oedema to poor renal blood flow secondary to the reduced cardiac output, and raised venous pressure to hydraemia and perhaps partly to bulging of the inter-ventricular septum into the cavity of the right ventricle, thus interfering with proper filling of that chamber (Bernheim effect). In a typical example cited, post-mortem examination of a patient showing such signs during life revealed a huge dilated left ventricle, a normal pulmonary artery, a small right ventricle, a normal tricuspid valve, and a large dilated right atrium, the cavity of the right ventricle being greatly reduced by the bulging inter-ventricular septum.

THE PROBLEM

During the 19th century mitral insufficiency was the valvular lesion most commonly diagnosed. Largely due to the teaching of Graham Steel[268] (1906), Sir James Mackenzie[269] (1916) and Lewis[270] (1933) the first half of the 20th century witnessed a diagnostic revolution; the fallacy of diagnosing organic mitral regurgitation on hearing a systolic murmur at the cardiac apex was stressed, and much unwarranted cardiac invalidism was thereby prevented. It was not however until the introduction of mitral valvotomy in 1948 demanded more accurate diagnosis, and investigators all over the world were stimulated to study the problem, that the disease was first seen in its proper perspective and its true incidence recognised.

On the basis of statistical evidence produced by Sir John Parkinson[271] in his Harvein oration of 1945, Wood[250] (1956) has deduced that the total incidence of rheumatic heart disease in persons between the ages of 18 and 44 in Great Britain during the period 1939 - 1945 must have been not less than 240,000, or 2.6% of the population in that age group. Since the mitral valve is involved in 85% of all cases of established rheumatic heart disease (Cabot[272] 1926), and since 28% of patients with rheumatic mitral disease suffer from mitral insufficiency of significant degree (Wood[273] 1954), it may be concluded that not less than 57,000 persons (or .53% of the population) in their prime of life were afflicted by a disease whose average prognosis from the time of onset of symptoms to total incapacity is 5.4 years (Wood[273] 1954). It is thus obvious that a suitable technique for the correction of this lesion is urgently required.

Despite a vast amount of work - both experimental and clinical - on the surgical correction of mitral insufficiency during the past 20 years, no entirely satisfactory treatment has been forthcoming, and the very variety of operations recommended indicates the ineffectiveness of most of the techniques which have been devised. This lack of success is hardly surprising however, when one considers that, prior to 1953, operations on the heart valves were of necessity performed by blind intra-cardiac manipulation without the interruption of the circulation.

The introduction during recent years of safe and efficient pump-oxygenator systems for the extra-corporeal oxygenation of blood, has enabled surgeons to visualise the diseased valve at operation, and the possibility of complete surgical correction of the defect has become greatly increased. Only two open-heart techniques however - the operation of "annuloplasty" described by Lillehei and his associates[181] (1957), - and the use of an Ivalon baffle (Gott et al.,[137] 1957) - have achieved any measure of clinical success. The first of these controls regurgitation which is primarily due to dilatation of the annulus fibrosus, but is of limited value in those cases of insufficiency due to an absolute deficiency of leaflet tissue. Regurgitation, the result of this latter type of defect, may in some cases be controlled by the use of an Ivalon baffle, but the complete correction of free mitral regurgitation due to gross deficiency of leaflet tissue awaits the development of a suitable mobile prosthetic valve (Lillehei[181] 1957).

Because of this small group of cases which, unfortunately, can be diagnosed only at operation, there is a tendency to regard surgery as a last resort, for the patient in cardiac failure with gross secondary myocardial changes, whose prognosis is in any case hopeless. The surgeon is unwilling to operate upon a patient during an early stage of his disease, only to find during the course of a major operation, that he is unable to correct the defect by techniques at present available.

The development of a suitable prosthesis will therefore, not only enable the surgeon to correct defects at present inoperable, but will also indirectly improve the prognosis in all cases, in that it will allow him to intervene at an earlier stage, before secondary pathological effects have developed, secure in the knowledge that he can correct any abnormality of the valve which he may encounter.

Before a prosthetic valve can be employed clinically for the correction of mitral insufficiency it must be demonstrated:

1. That the prosthesis is easy to insert and secure in the desired position within the heart.
2. That the prosthesis is mechanically effective, that

is, it must correct regurgitation but not cause stenosis.

3. That the prosthesis is durable. At 70 beats per minute the heart beats 100,800 times daily; a prosthetic valve must therefore open and close over one million times every 10 days and the material from which it is fabricated must be able to tolerate the motion and hydrostatic forces to which it will be subjected.

4. That the prosthesis is tolerated within the circulation, that is, is not extruded as a foreign body, and that it does not damage the elements of the blood or promote thrombosis or embolisation.

The problem confronting the investigator is to develope a prosthetic valve which will satisfy the above criteria.

A RATIONAL APPROACH TO THE PROBLEM

A detailed study of the complex anatomy of the normal mitral valvular apparatus and its relationships, indicated that 6 anatomical features should be taken into account when considering the placement and design of a prosthetic valve for the correction of mitral insufficiency:

1. The mitral annulus fibrosus constitutes a convenient fibrous band and the only intra-cardiac structure in this region, which may reasonably be expected to tolerate sutures without their cutting through.
2. The antero-medial portion of the mitral annulus is irregular in shape, being bi-concave when viewed from the auricular aspect, and is intimately related to the root of the aorta and the origin of 2 cusps of the aortic valve (Figs. 2,3.).
3. The aortic leaflet of the mitral valve is the only dividing structure between the aortic and mitral orifices, and constitutes an intergral part of the left ventricular outflow tract (Fig. 4).
4. The postero-lateral portion of the annulus is intimately related to terminal branches of the circumflex coronary artery, the proximal portion of the great cardiac vein, and the coronary sinus.

5. The square area of the postero-lateral cusp is but 1/3 the total leaflet tissue area.

6. The chordo-papillary system is an intricate and delicate anatomical structure, the imitation of which by artificial structures appears to be impractical.

As a result of these observations it was concluded that a prosthetic valve could be most safely and securely fixed to the annulus fibrosus of the valve. In order to avoid any interference with the cusps of the aortic valve, the root of the aorta, or the left ventricular outflow tract, sutures should be confined to the postero-lateral sector of the annulus, and carefully and superficially placed so as to avoid damage to the vessels which are related to this portion of the ring. The small surface area of the postero-lateral cusp suggested that it plays a relatively minor role during normal valve closure, and it was apparent that by replacing this leaflet with a prosthetic device, whose surface area in the closed position is greater than that of the normal, compensation for a deficiency of leaflet substance of the remaining cusps could readily be effected.

A study of the mechanism of action of the normal mitral valve revealed that:

1. The valve leaflets are activated mainly by haemodynamic forces.

2. The postero-lateral cusp undergoes a relatively small degree of excursion, and plays a minor (yet nevertheless

important) role during valve closure (Fig. 10).

3. The delicate chordo-papillary system restrains the leaflets during ventricular systole, thus preventing their eversion into the atrium (Fig.9).

4. The annulus fibrosus acts as a "sphincter", undergoing contraction during systole and relaxation during diastole.

It appeared therefore, that a simple flap-type prosthetic valve, fixed to the postero-lateral portion of the annulus, would be activated by the haemodynamic forces normally active within the chambers of the left side of the heart. In view of the difficulty of imitating the chordo-papillary system, that is, anchoring any structure to the ventricular myocardium, any such prosthetic valve should be so designed as to resist eversion into the atrium during systole, by virtue either of its strength or structural shape. In order to preserve as much as possible of the sphincter action of the valve ring, it was concluded that the prosthesis should not occupy too great an arc of the latters circumference. Any form of "ring" prosthesis fixed to the annulus must, if rigid prevent, or if pliable become distorted by, the systolic contraction, and for this reason, as well as the anatomical considerations already mentioned, was considered to be unsatisfactory.

The clinical picture of mitral insufficiency may be the result of a diversity of pathological lesions (Figs 11 - 15), and it would appear that no single method of correction can be applied to all cases (Barnard, McKenzie and Schrire [140] 1960). Definitive surgical treatment must depend on an accurate assesment of the pathological anatomy of the diseased valve at operation, and this can only be achieved by direct vision surgery. Perforated or cleft cusps can then be repaired by simple plastic procedures, the mobility of fixed leaflets can be restored by commissurotomy, decalcification, or freeing of chordo-papillary adhesions, annular dilatation can be corrected by annuloplasty, an Ivalon baffle can be inserted in suitable cases and prosthetic replacement can be reserved for those cases with a gross deficiency of leaflet tissue.

A simple flap-type valve, fixed to the posterior-lateral portion of the valve ring such as we envisaged, appeared to be capable of compensating for a deficiency of leaflet substance. In addition, a valve secured as suggested, should not prevent the reversal of functional dilatation of the valve ring which is thought to occur once regurgitation has been corrected. Should the circumference of the annulus become decreased post-operatively, and should the prosthetic valve not be displaced or distorted thereby, its efficiency would be expected to increase with time.

On the basis of the above observations it was decided that a"flap-type" valve which could be fixed to the postero-lateral segment of the annulus fibrosus, and whose strength or structural design would prevent eversion into the atrium during systole, would be designed and tested.

MATERIALS

The choice of material from which to fabricate a prosthetic valve is of vital importance, as the fulfilment of several of the criteria which any prosthesis must satisfy before it may be employed clinically, is primarily dependent upon the properties of the material used. A flap-type valve must be flexible and pliable so as to become moulded to the contour of the structures against which it will close during systole, and to move freely under the influence of the haemodynamic forces by which it is activated. In addition, the material must be strong enough to withstand the millions of systolic poundings to which the valve will be subjected, it must not be rejected as a foreign body by the patient's tissues, it must not damage the elements of the blood and it must not promote thrombosis or embolisation.

Two groups of materials - some form of tissue graft or certain artificial materials - could conceivably fulfil these criteria.

(i) Tissue Grafts.

The use of tissue grafts for the correction of various intra-cardiac defects has been thoroughly investigated by numerous previous workers (Wilson[114] 1930; Murray et al.,[110] 1938; Bailey et al.,[116] 1951; Moore and Shumacker[113] 1953; Glover et al.,[119] 1953; Tedeschi and Nahas[120] 1955.). Free grafts, both autogenous and homologous (Brewin[117] 1956; Murray[128] 1956) and vascularised pedicled grafts (Bailey et al.,[116] 1951.[123] 1954; and Henderson et al.,[124] 1953.), have been employed, and while many of these experiments have shown early promise, later results have been disappointing due to fibrosis, contraction or fragmentation of the grafts.

In view of the uniformly unsatisfactory results recorded by these investigators, it was decided not to attempt the use of tissue grafts, but to concentrate on an artificial material for the fabrication of the prosthetic valve.

(ii) Artificial Materials.

Numerous artificial materials have been placed within the chambers of the heart, among which may be listed Stainless-steel (Berg et al.,[144] 1957), Lucite (Harken et al.,[133] 1954), Plexiglass (Benichout and Chalmot[135] 1955) Polyethyline (Johns and Blalock[141] 1954), Teflon (Kerman et al.,[145] 1957), Nylon (Jordan and Wible[142] 1955), Ivalon (DeWall et al.,[154] 1956), Mylar (Barnard[274] 1958), and Silastic (Barnard[274] 1958; Ellis and Bulbulian[146] 1958). Of the materials mentioned, only those which are flexible were considered, and after a thorough study of the properties of each, and the results and observations of previous investigators, it was concluded that Silastic - a silicone-rubber compound - would prove to be the most suitable substance from which to fashion a prosthetic flap-type valve.

Silicone-rubbers are prepared from Silicone metal and organic chloride compounds such as methyl chloride to produce methyl chlorosilaner, which is one of a group of possible intermediate organo-chlorosilanes. The final organopoly siloanes are compounds containing a skeleton of alternating silicone and oxygen atoms, with side chains of organic molecules attached to the silicone molecules.

The physical properties of silicones depend on the detached molecular structure of the molecules, and they can exist as fluids, rubbery silastic compounds or thermo-set resins. The Silastic elastomers are linear polymers of high molecular weight, that are capable of vulcanisation. The major properties of the Silicone rubbers are:-

a) Resistance to extremes of temperature (- 150F to 600F.).

b) Superior resistance to compression set throughout the operating temperature range.

c) Unequaled resistance to ozone, ageing, and sunlight.

d) Good chemical resistance, making them odourless, tasteless, non-corrosive, non-staining and non-sticking.

When heat-cured, Silastic is a tough, pliable, elastic substance, which is not apt to lead to clot formation if fixed to the mitral ring (Ellis and Bulbulian[146] 1958), or if allowed to flap freely within the circulation (Barnard[274] 1958). In vitro studies have demonstrated that the material is extremely tough, a strip having been flexed through 90°, 100 million times, without showing any signs of wear (Barnard[274] 1958).

The only obvious disadvantages of Silastic are that it does not permit the ingrowth of host tissues, and that sutures tend to "cut through". These disadvantages may be overcome by moulding strips of compressed poly-vinyl sponge - which leads to a firm union with the mitral annulus, and which prevents sutures from "cutting through" - to that portion of the prosthesis which will be sutured to the annulus.

EXPERIMENTAL METHODS AND RESULTS

A. Method of fabricating Silastic valves.

The details of mould construction for the fabrication of Silastic valves are beyond the scope of this thesis, but briefly the method employed is as follows:

A metal copy or pattern is fashioned by hand from a design (Fig. 16) or model of the particular valve to be fabricated. Using this metal model as a "pattern", a plaster-of-paris mould is poured, and the shape of the latter is then impressed into special moulding sand. The final metal mould is produced by pouring molten metal (aluminium at 700 C) into the sand mould. A 2 mm. diameter injection hole, and a finer "bleeder" hole are then drilled at suitable points, and the surfaces of the mould are polished to a mirror finish (Fig. 17).

To make a valve, a 5 ml. capacity stainless-steel syringe is filled with raw Silastic, which is injected into, the mould under pressure, until it begins to escape from the bleeder hole. The mould is subjected to steam-heat at a temporature of 259° F and a pressure of 20 lbs. per sq. inch for 5 minutes. The valve may then be removed from the mould and is then cured in an oven at a temporature of 300° F for 2 hours. After curing, the valve is inspected for air bubbles or other obvious defects, before being subjected to tests of function or durability, or inserted into experimental animals.

In order to devise a mechanically effective prosthesis, it

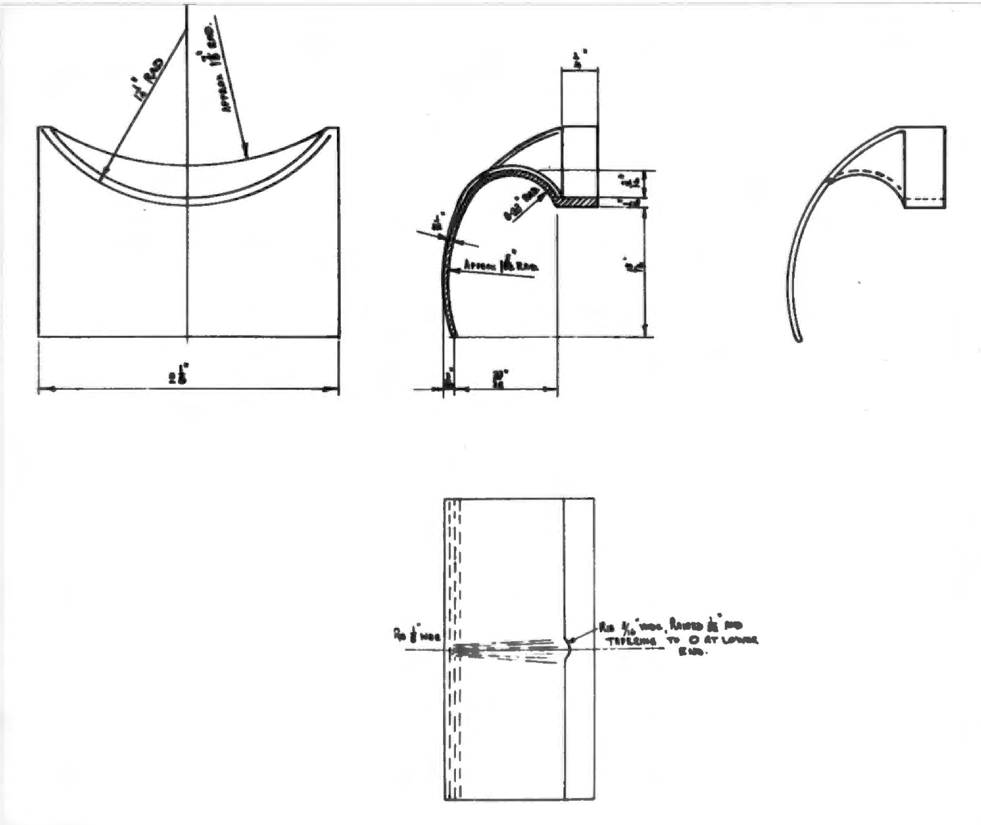


FIGURE 16. Photograph of the original scale design used for the fabrication of Silastic Valve 11.

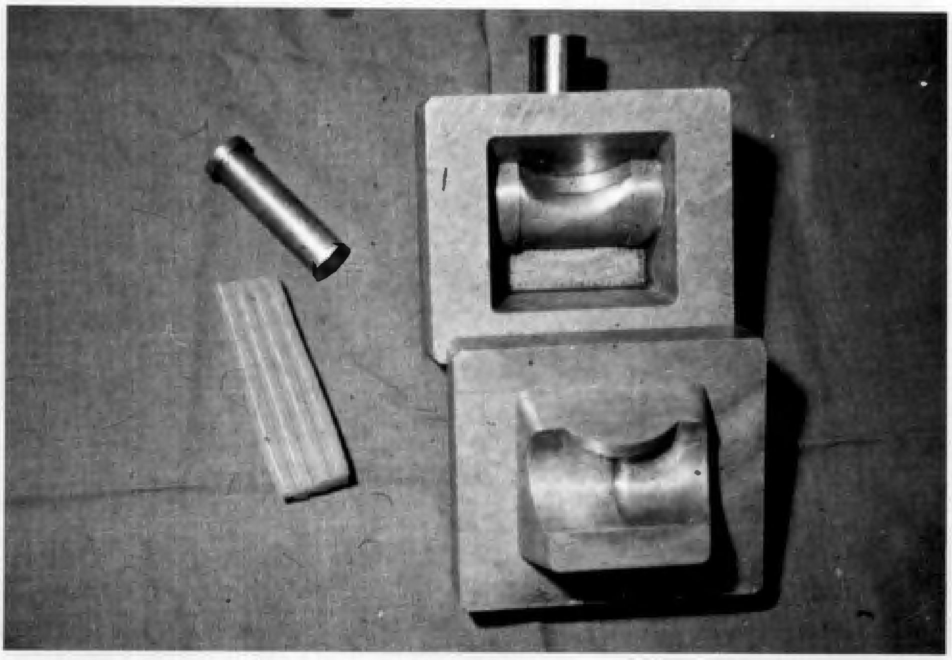


FIGURE 17. The metal mould and syringe used for the manufacture of Silastic Valve 11, together with a specimen of raw Silastic.

was realised that several different valve designs, with minor or major modifications of each, would have to be studied. The manufacture of a single metal mould, however, is a time-consuming and expensive process, and the production of such moulds for experimental purposes soon proved to be impracticable. An alternative method of manufacturing valves of similar consistency, pliability and elasticity for test purposes, was therefore necessary, and a technique using Revultex - a liquid latex-rubber - was devised.

B. Method of fabricating Latex-rubber valves, and the experimental valvue of such valves.

A "positive" mould of the desired shape and size is carved by hand from a block of plaster-of-paris (Fig. 18), and several coats of liquid latex-rubber (Revultex) are painted on the mould with a fine paint brush. Each coat of latex is allowed to dry completely before the next coat is applied, and the drying process may be accelerated by subjecting the mould to a jet of cold air. Warm air must not be used as this causes the latex to shrink, and the valve becomes distorted when removed from the mould. The thickness of each valve will depend on the number of coats of latex applied, and in practice it has been found that 20 coats result in a thickness of approximately 1mm.

As compared with a strip of cured Silastic of equal dimensions, latex is slightly less pliable and flexible, but has a greater degree

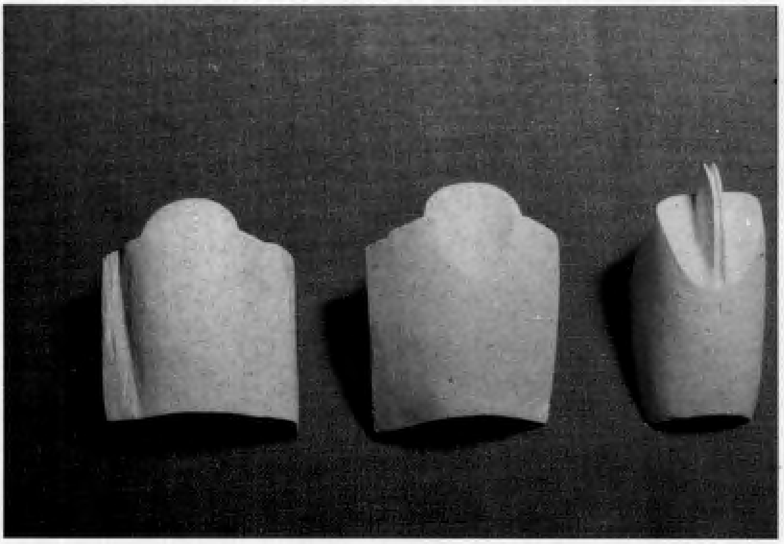


FIGURE 18. Three examples of the plaster-of-paris moulds used for the manufacture of latex-rubber valves.

of elasticity. Despite these differences in the properties of the two materials, the manufacture of the latex valves proved to be of inestimable valvue for the investigation of valve design, as a variety of latex valves of assorted sizes and shapes could be rapidly and inexpensively produced, and their action studied in the artificial pulse-duplicator. Those designs which on testing proved to be unsatisfactory, were discarded, while modifications of other more promising designs were easily effected as indicated. Only once a satisfactory latex valve had been designed was a metal mould for the fabrication of Silastic valves of similar design manufactured. By using this technique much valuable time was saved, and the expenses of fabricating Silastic valves of a design which, when tested, would prove to be unsatisfactory, were avoided.

C. Method of testing and studying valve action in vitro - the Pulse-Duplicator.

In order to study the action of the normal mitral valve leaflets, and also to study and test the action and efficiency of prosthetic valves designed for the correction of mitral insufficiency, without having recourse to experimental animals, a simple electrical artificial pulse-duplicator, based on the work of McMillan et al.,[275] (1952); McMillan[276] (1955); and Davila et al.,[277] (1956) was designed (Barnard McKenzie and de Villiers[278] 1959).

1. Apparatus.

The apparatus consists of:-

(a) Two electrically activated, one inch diameter, solenoid

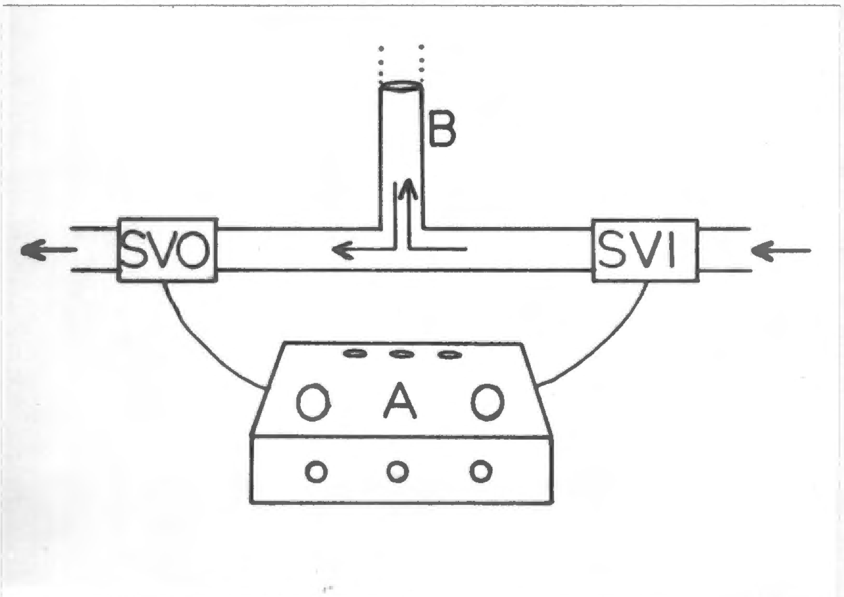


FIGURE 19. Diagram of the electrical pulse-duplicator.

magnetic valves, which are connected in series as shown in Fig. 19. The inlet valve SVI is connected by means of a length of plastic tubing to a water faucet, the outlet valve SVO leading to a water drain. The electrical circuit (Fig. 20) is so constructed that:

(i) the inlet and outlet valves act reciprocally, i.e., the outlet valve closes when the inlet valve opens and vice versa.

(ii) the number of cycles per minute may be controlled by a switch on the control box (Fig 19 A) - the range of the apparatus described is 70 - 150 cycles per minute.

(iii) the ratio of systole : diastole per cycle may be controlled by a second switch on the control box (Fig. 19 A).

(b) A polished Plexiglass viewing chamber (Fig. 21) which is fixed within the left atrium. This chamber is a flattened cylinder 12 cms. in diameter and 4 cms. high. Adjacent to the circumferential margin of its inferior surface a conical funnel, one cm. long, and of internal diameter 3 cms. above and 3.3 cms. below, opens into the chamber; diagonally opposite to this, and on its superior surface, a cylindrical funnel 4.5 cms. high, and 2 cms. in internal diameter similarly

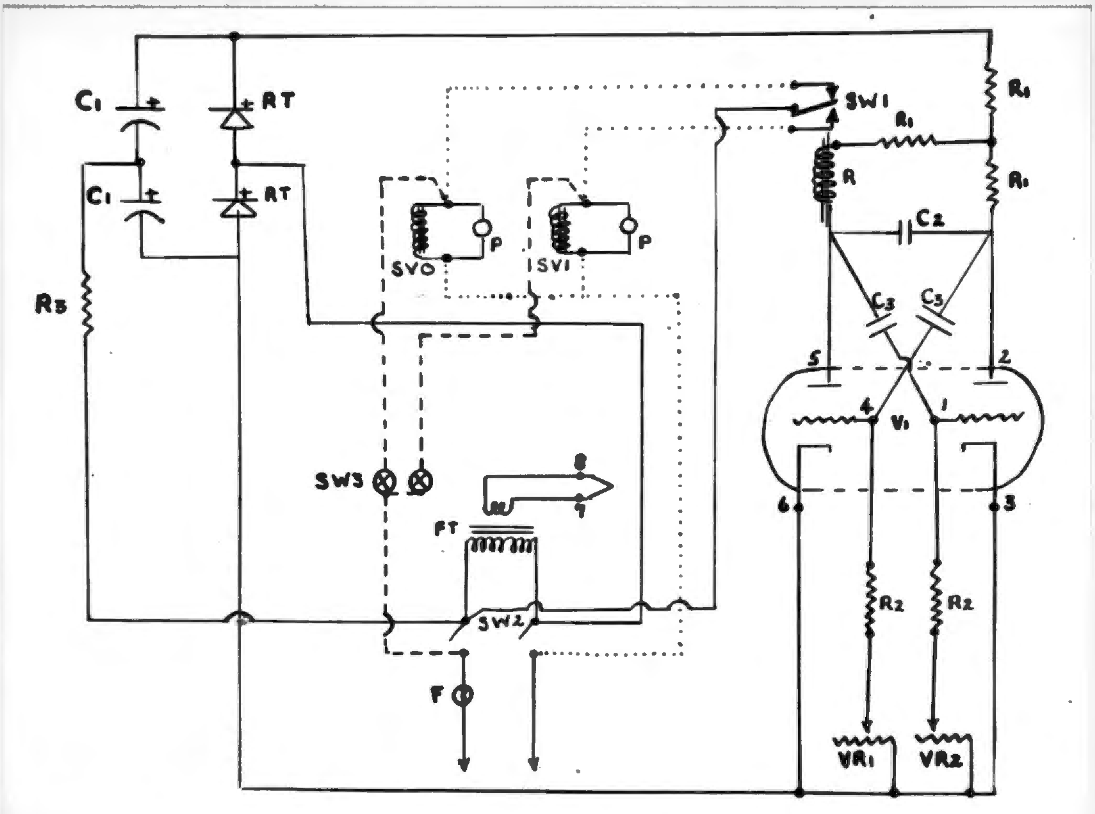


FIGURE 20. Electrical pulse-duplicator circuit diagram.

R	-	relay
RT	-	rectifiers
R1	-	10,000 ohm resistors
R2	-	.1 megohm resistors
R3	-	47 ohm resistor
P	-	pilot lamp
F	-	fuse (3 amperes)
FT	-	filament transformer
SVI	-	inlet solenoid valve
SVO	-	outlet solenoid valve
VR1	-	200,000 ohm rheostat
C1	-	capacitor (electrolytic)
C2	-	.1 microfarad 600 volt capacitor
C3	-	1 microfarad 600 volt capacitor
SW1	-	single throw, single pole switch
SW2	-	single throw, double pole switch
SW3	-	push-button switch
V1(1-8)	-	valve base sockets for type 6Sn7 radio valve (double triode-separate cathodes - octal base valve.

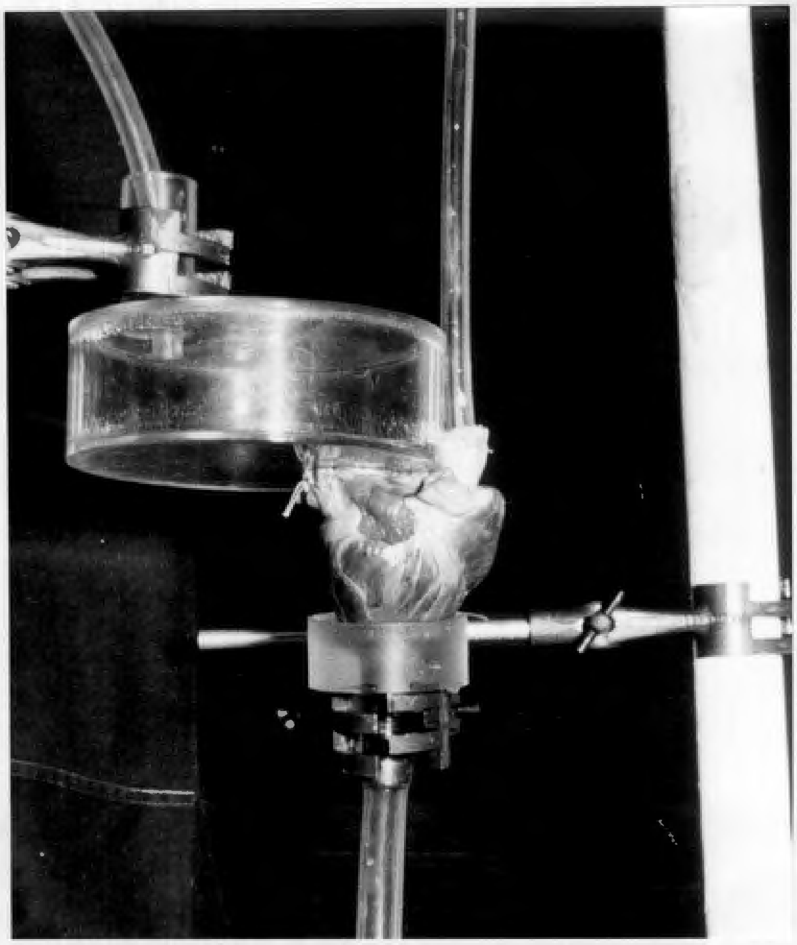


FIGURE 21 (a). Photograph of an heart set up in the pulse-duplicator showing plexiglass viewing chamber and filling tube, plexiglass supporting block, inlet tube screwed into the apex of the left ventricle, Mayon tubing tied into the root of the aorta, and metal supporting clamps.

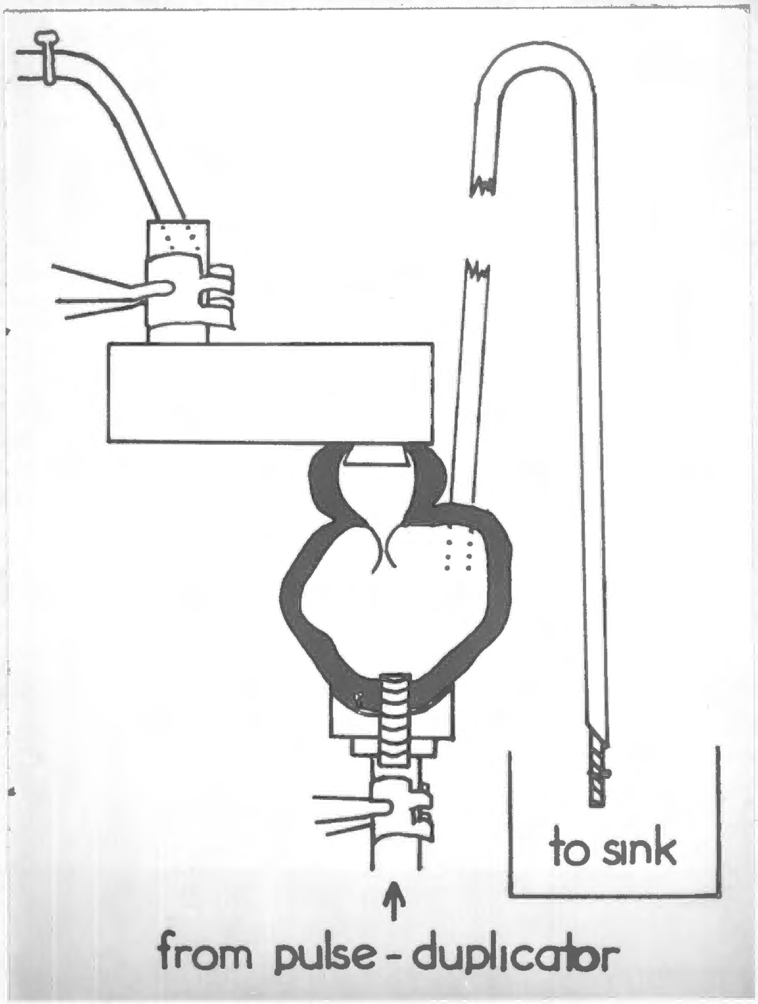


FIGURE 21 (b). Diagrammatic representation of heart set up in the pulse-duplicator (Fig 21 a).

opens into the chamber.

(c) A cylindrical Plexiglass block upon which the heart is supported, and through which a metal tube passes to enter the apex of the left ventricle (Fig. 21). The Plexiglass cylinder 2.5 cms. thick and 6 cms. in diameter, is "saucered" on its superior surface so as to accomodate the contour of the cardiac apex when in position. A central hole 1.1 cms. in diameter transmits a 5 cm. long brass tube of internal diameter .8 cms. the outer surface of which has a screw "thread". A small Plexiglass disc with reciprocal thread is screwed onto this tube and locks the cylindrical block in position. The proximal end of the brass tube is connected to the fluid system of the pulse duplicator (Fig. 19 B) by means of a short length of plastic tubing.

(d) Adjustable metal clamps which support the components of the pulse-duplicator (Fig.21).

2. Preparation of the Heart.

Fresh human hearts removed at autopsy are used to study the action of the mitral valve.

The roof of the left auricle is excised below the entrance of the pulmonary veins. The left atrial appendage is ligated at its base, and a linen "purse-string" suture is placed around the circumference of the auricular defect, through which the conical funnel of the plexiglass viewing chamber will later be introduced.

The root of the aorta is dissected free from the pulmonary artery, and the vessel is transected approximately 5 cms. from its origin. A "purse-string" suture is placed about its circumference, just proximal to the level of transection.

The apex of the left ventricle is excised until the cavity of that chamber is entered, and a thick linen "purse-string" suture is placed about the cardiac apex.

If an artificial valve is to be studied, such a valve may then be sutured in the desired position, and the heart is ready to be set up in the pulse duplicator.

3. Assembling the Pulse Duplicator.

Metal stands and clamps as shown in Fig 21 are placed in position. One end of a 12 inch length of 3/8 inch internal diameter plastic tubing is connected to the fluid system of the pulse duplicator, the opposite end being connected to the threaded brass tube. The latter, with its Plexiglass locking disc and Plexiglass saucered block in position, is screwed into the hole in the left ventricular apex, and the "purse-string" suture is drawn tight and tied. The heart is then supported on the Plexiglass block which is held in position by one of the metal clamps.

The conical funnel which protudes from the inferior surface of the viewing chamber is inserted into the left atrium, and the "purse-string" suture already in situ is tightened and tied. The viewing chamber is then clamped in such a position that the heart lies suspended vertically between it above, and the saucered Plexiglass block below (Fig. 21)

The ascending limb of an inverted plastic U-tube, of suitable bore, is tied into the aorta by means of the"purse-string" suture surrounding that vessel. The height of this limb is so adjusted that when filled with water, it will exert a pressure on the aortic valve equal to the normal diastolic pressure. The descending limb of the U-tube is encircled by an adjustable occluding clamp, and led off to a drain.

A length of 1/4 inch bore plastic tubing leading from a water source, is inserted into the funnel protruding from the upper surface of the viewing chamber, and serves to maintain the water level in that chamber during operation(Fig. 21).

4. <u>Operating the Pulse Duplicator</u>.

The solenoid magnetic valves are switched on and the "heart rate" and systole/diastole ratio are adjusted as required by means of the switches on the control box (Fig. 19 A).

The water faucet which provides the pressure in this artificial system is turned on. With each "beat" of the pulse duplicator, the inlet solenoid opens, the outlet solenoid closes, and water under pressure (the pressure-head depending upon the degree to which the water faucet is opened) is forced into the left ventricle of the heart. The intraventricular pressure therefore rises during simulated systole, exceeds the hydrostatic pressure of the column of water in the viewing chamber, and the mitral valve cusps close. As the intraventricular pressure continues to rise during systole, the aortic diastolic pressure is exceeded, the aortic valve opens, and water is ejected via the "aorta".

During diastole the inlet solenoid valve closes, the outlet valve opens, water flows out of the ventricle and the intraventricular pressure falls below the aortic diastolic pressure. The aortic valve therefore closes. As diastole progresses the hydrostatic pressure of the water in the viewing chamber i.e. the simulated left atrial pressure, exceeds the intraventricular pressure, the mitral valve opens and water flows from the latter chamber into the ventricle.

The diastolic loss of fluid from the viewing chamber into the ventricle, is compensated for by the constant addition of water via the upper funnel of that chamber (Fig. 21). It is essential that the fluid level in this chamber be maintained during cine photography of the valve, in order to avoid the presence of bubbles or a receding water meniscus, which may impair visibility.

Once the pulse duplicator is functioning satisfactorily, a pressure recording device is introduced into the plastic tube leading to the ventricular cavity. By partially occluding the descending limb of the "aorta", and adjusting the water faucet which supplies the water pressure in the system, a ventricular systolic pressure equal to that normally present within the left ventricle can be achieved. By measuring the volume of water ejected from the aortic U-tube in unit time the output of the system can be calculated.

D. Method of testing durability of prosthetic valves.

That Silastic is able to withstand millions of simple flexions without any signs of wear, has already been demonstrated (Barnard[274] 1958). The stresses which any particular valve will have to tolerate however, will depend both on the design of the valve and also the pressures which act upon it. It was apparent therefore, that each design of prosthesis would have to be independantly tested for durability before being employed clinically, and that any test devised should aim at subjecting the valve to stresses and motions similar to those which it would have to undergo when placed within the beating heart.

In order to test the durability of a simple flap type valve, the pulse duplicator (Fig. 19) was connected to a testing chamber as depicted diagramatically in Fig. 22. The latter consists of 2 chambers, A and B, separated from one another by a rigid disc, the 3 components of the apparatus being held together by circumferential screws. The only communication between the 2 chambers is through a central hole in disc C. An inverted plastic U-tube, fitted with an adjustable occluding clamp, represents the aorta and leads from chamber A to a water drain. An inlet funnel F connects chamber B to an adjustable water supply, and represents the pulmonary venous flow. By connecting a pressure recording apparatus to the nipple (Fig. 22a) on chamber A, the pressure changes generated during the pulse duplicator cycle may be recorded.

The valve to be tested is sutured to one half of the circumference

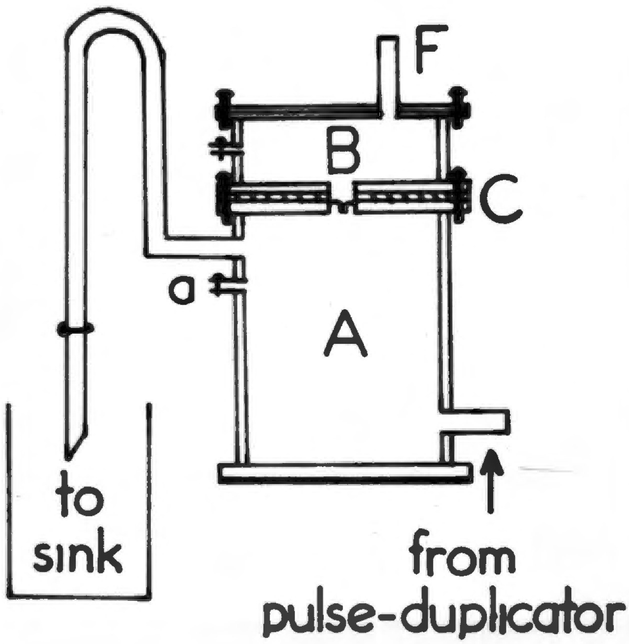


FIGURE 22. Diagram of testing chamber used to test the durability of simple flap valves.

of an oval hole, of suitable size, cut in a piece of compressed poly-vinyl sponge, which is clamped to disc C so that the valve overlies the hole in the latter. On turning on the pulse duplicator, the pressure in chamber A rises, exceeds that in chamber B and fluid tends to flow from A to B, via the hole in disc C. The flap type valve is therefore closed by fluid current. As the pressure in A continues to rise the pressure of the column of fluid in the ascending limb of the inverted plastic U-tube is exceeded, and fluid flows from A to a drain. During diastole the pressure in chamber A falls, the direction of flow in the aortic U-tube is reversed, fluid flows from chamber B to chamber A and the valve flaps open. The diastolic loss from chamber B, is compensated for by the constant addition of fluid via the inlet F.

By adjusting the volume of fluid injected into chamber A with each beat of the pulse duplicator, the height of the inverted U-tube, and the resistance to flow through the latter, the "ventricular" systolic pressure can be adjusted to equal that normally acting on the mitral valve.

E. Method of insertion of prosthetic valves in experimental animals.

The decision to replace a diseased mitral valve by a prosthetic device, can be made only after a careful assessment of the pathological anatomy of the abnormal valve, under direct vision at operation. In addition, the satisfactory action of a mechanically efficient valve is, in part, dependant upon its fixation in the correct position within the heart, and this is most likely to be accurately effected if a direct vision technique is employed. It was therefore decided that all experimental.operations should be performed under direct vision utilising the Helix-reservoir bubble oxygenator (DeWall et al.,[23] 1956), an oxygenator with which we had had considerable previous experimental (McKenzie and Barnard[279] 1958, [280] 1960) and clinical (Barnard, McKenzie et al.,[138] 1959)experience.

1. The problem of systemic air-embolism during open left atriotomy.

The occurence of systemic air-embolism during open left heart surgery has recieved much attention (Kay et al.,[185] 1958, Nichols et al[281] 1958; Miller et al.,[282] 1954),and recent interest in the direct vision correction of mitral insufficiency (kay et al.,[283] 1958, Lillehei et al[181] 1957; [136] 1958; Effler et al.,[193] 1958) utilising one or other method of extra-corporeal oxygenation, has resulted in an increasing awareness of this complication, and the problem of its prevention. Should the heart continue to beat during the performance of open left atriotomy, the danger of air bubbles entering the left ventricle and being pumped into the aorta is constantly present; at the time of closure of such an incision, whether in the still or beating heart, air bubbles may be trapped within the ventricle, atrium or pulmonary veins. In order to overcome these problems, numerous techniques have been described.

Miller et al.,[284] (1953) recommended the use of a multi-perforated plastic vent, placed within the left ventricle through a stab wound in the avascular portion of the apex. Blood and air was then continuously aspirated under a negative pressure of 10 to 20 cms. of water, and returned directly to the oxygenator. Their experimental results being satisfactory the method was employed clinically (Miller et al.,[282] 1954), and later Bahnson et al.,[285] (1957) successfully used such a vent during the removal of a left atrial myxoma. Levowitz et al.,[286] (1956) however, on the basis of animal experiments, concluded that the introduction of a ventricular vent did not provide complete protection from air-embolism, 4 of their 13 experimental animals suffering from this complication.

The introduction of gaseous carbon-dioxide to displace the air contained within any opened cardiac chamber, before permitting the blood to well up from the interior as the chamber is closed, was suggested by Nichols et al.,[281] (1958) and this technique was employed in 22 cases without untoward effects. Prior to this report, Moore and Braselton[287] (1949) had demonstrated that doses of 3 ml. of carbon dioxide per Kg. body-weight could be safely injected into the pulmonary veins of cats, and Stauffer et al .,[288] (1956) injected 7.5 ml. carbon-dioxide per Kg. body-weight into an infants ante-cubital vein, for X-ray visualisation of the cardiac chambers, without any appreciable effect other than transient apneoea. This gas is approximately 20 times as soluble in blood as is air, and is entirely taken up by blood within 20 seconds. Thus any bubbles of air which may be trapped within the heart are displaced by the carbon dioxide, which is so rapidly absorbed as to be clinically innocuous.

Lillehei et al.,[181] (1957),[136] (1958). Merendino and Bruce[182] (1957), and Effler et al.,[193] (1958) have performed left atriotomy on the beating heart without the occurence of air-embolism. Their success was attributed, in part, to the use of a right thoracic approach to the left atrium, and in part to the maintenance of incompetence of the mitral valve during the intracardiac manipulations. A right-sided approach, with the patient in the lateral position, or with the right shoulder elevated 30 degrees, ensures that the left ventricle is in a dependent position, and that the atriotomy incision is above thelevel of the mitral valve. The maintenance of valvular incompetence prevents the intraventricular pressure from exceeding the aortic perfusion pressure, and hence the pumping of air into the systemic circulation.

Despite similar precautions however Kay et al.,[283] (1958) reported the occurence of systemic air-embolism in 3 of 24 patients subjected to direct vision surgery for the correction of mitral insufficiency, Guidry et al.,[289] (1958) reported episodes suggestive of cerebral air-embolism in 2 of 6 patients subjected to direct vision mitral annuloplasty, and coronary air-embolism (successfully treated) occured in one of 2 patients on whom we have performed left atriotomy under direct vision (Barnard, McKenzie et al.,[138] 1959). In addition, several experimental animals subjected to direct vision left atriotomy using this technique have shown clinical evidence of cerebral air-embolism post-operatively.

Induced cardiac arrest as advocated by Melrose et al.,[99] (1955) in an accepted adjunct to open heart surgery, and has been extensively used clinically for operations on both the right (Effler et al.,[290] 1957), and the left side (Kay et al.,[283] 1958; Effler et al.,[193] 1958) of the heart. The use of this technique for the performance of left atriotomy, prevents the occurence of air-embolism during the course of the intracardiac manipulations, but the problem of expelling the air from the cardiac chambers prior to closure of the atriotomy remains, and Kay et al.,[283] (1958) have reported an instance of transient cerebral air-embolism in a patient subjected to cardiac arrest during the direct vision correction of mitral insufficiency. The method requires occlusion of the aorta above the coronary ostia, with the consequence that the hypertrophied left ventricle is denied the benefit of continuous perfusion. Also, as Lillehei[136] (1958) has pointed out, it is difficult to evaluate the diseased mitral valve, or to judge when competence of the valve has been restored, in the absence of a heart beat.

Senning[291] (1952) suggested the use of elective ventricular fibrillation for the prevention of air-embolism during open left heart surgery, and Kerman et al.,[145] (1957) and Kaplan et al.,[292] (1958) in animal experiments, and Crafoord[293] (1955) and Levowitz et al.,[286] (1956) in operations on patients, have subsequently employed a similar technique successfully. In view of the apparent simplicity and safety of this method and in spite of the disadvantage of a still heart during mitral valve surgery, it was decided to investigate the use of this technique as a means of preventing systemic air-embolism during the direct vision insertion of a prosthetic mitral valve.

2. <u>Elective ventricular fibrillation for the prevention of systemic air-embolism during open left atriotomy.</u>

A series of experimental operations was performed in order to establish a method of inducing fibrillation, to test its reversibility, and to study the effectiveness of this technique as a means of avoiding systemic air-embolism (McKenzie and Barnard[230] 1960).

Twenty unselected mongrel dogs, weighing 13 - 21 Kg., were subjected to right thoracotomy and total cardio-pulmonary by-pass using the Helix-reservoir bubble oxygenator. All animals were perfused at a flow-rate of 70 ml. per Kg. body-weight per minute. Ventricular fibrillation was induced by means of a shock from a 6 volt D.C. stimulator, with a pulse frequency of 70 cycles per second, and pulse duration of 100 microsecs. The electrical current was applied to the surface of the ventricular myocardium by means of two closely spaced point electrodes, a 1 - 3 second contact being neccessary to induce fibrillation which was not spontaneously reversible. Defibrillation was accomplished with a counter-shock of 135 volts for .1 second, through two 4 cm. diameter circular copper electrodes, applied to opposite sides of the ventricular myocardium.

It was found that the optimal distance between the two point electrodes of the fibrillating apparatus is approximately ½ m.m. If the two electrodes are placed further than 2 mms. apart, there is no demonstrable effect on cardiac rhythym, and a contact of longer than 5 seconds duration results in a small myocardial burn. Once ventricular fibrillation is established spontaneous reversal to normal sinus rhythm does not occur.

Four of the animals were subjected to right atriotomy, 6 to right atriotomy and ventriculotomy, and 10 to right atriotomy and left atriotomy, and fibrillation was allowed to continue for periods ranging from 15 to 52 minutes, before normal sinus rhythm was re-established.

During the course of those operations at which a left atriotomy was performed, it was noticed that air-bubbles tended to collect within the terminal portions of the pulmonary veins, and in order to evacuate these, it was neccessary to temporarily reinstitute gentle respiratory movements just prior to closure of the left atrial incision. So as to prevent any air from becoming trapped within the ventricular cavity, the left heart was allowed to fill with blood while incompetence of the mitral valve was maintained, and closure was effected only after all air-bubbles had been expelled. On no occasion was any difficulty experienced in reversing ventricular fibrillation. Of the 10 animals subjected to right cardiotomy, one died of infection on the 6th post-operative day, and one died on the operating table, the result of an error in anaesthetic technique. The remaining 8 dogs survived normally, their immediate post-operative and subsequent behaviour resembling in every way that of a similar series of experimental animals, in which ventricular fibrillation was not induced (McKenzie and Barnard[279] 1958). Of the ten animals subjected to left atriotomy, one died 48 hrs. post-operatively, the result of rupture of the atriotomy incision. None of the survivors showed any clinical evidence of systemic air-embolism, their post operative course resembling that of the animals subjected to right cardiotomy only.

As a result of these experiments it was concluded that elective ventricular fibrillation is a safe and effective method of preventing systemic air-embolism during open left-heart surgery, and this technique was employed in all subsequent experimental operations on the mitral valve.

3. <u>The surgical approach to the mitral valve.</u>

It is generally considered that the left atrium is best approached via the right hemi-thorax, when direct vision surgery of the mitral valve is contemplated (Lillehei et al.,[181] 1957; [136] 1958; Kay et al.,[185,283] 1958, Effler et al.,[193] 1958). Access to the valve may then be obtained by an incision in the posterior wall of the left atrium (Lillehei et al.,[181] 1957), or through the fossa ovalis by way of the right atrium (Effler et al.,[193] 1958). Such an approach is thought to be preferable to a direct left-sided attack when extra-corporeal circulation is to be employed, as the neccessity for bi-lateral thoracotomy, which would otherwise be neccessary (as the right hemi-thorax must be exposed for the insertion of the caval catheters) is obviated. In addition, as has been previously discussed, the dependent position of the left ventricle during right thoracotomy is thought to decrease the liklehood of occurence of systemic air-embolism.

In our early experiments therefore, a right thoracotomy was performed, and the mitral valve was exposed via the posterior wall of the atrium or the inter-atrial septum. Because of the small size of the left atrium of the normal dog, the operation was found to be technically difficult, and although it was possible to visualise the valve, and to insert a prosthesis in the correct position, the technique was abandoned in favour of a direct left-sided approach. The use of the latter approach necessitated a modification in the technique of caval catheterisation, but it was found that visibility was greatly improved, the fixation of prosthetic valves was found to be technically easier, and the duration of total cardio-pulmonary by-pass neccessary for the intra-cardiac manipulations, was reduced by about 30 minutes.

A limited clinical experience of open left atriotomy via the right hemi-thorax (Barnard, McKenzie et al.,[138] 1959; and Barnard, McKenzie and Schrire[140] 1960), has shown that in a patient with an enlarged left atrium, exposure of the mitral valve is adequate, and a left thoracic approach is reccommended only for animal experiments.

4. Experimental operative technique.

Anaesthesia in the unpremedicated animal is induced with intravenous thiopentone, a cuffed endotracheal tube is inserted, and manual intermittent positive-pressure respiration of a nitrous oxide-oxygen mixture is instituted. During the course of the operation, fractional doses of thiopentone are administered as indicated.

With the animal in the right lateral position, the left hemi-thorax is entered via the periosteal bed of the resected 5th rib and costal cartilage (Fig 23 a). Particular care is taken with haemostasis all bleeding points being coagulated with diathermy. A "T" shaped pericardial incision is then made, (the horizontal limb of the "T" running parallel and anterior to the left phrenic nerve (Fig. 23b), the vertical limb running from left to right at right angles to the latter) and the left chambers of the heart are freely exposed (Fig 23 c). The animal is then heparinised (1.5 mgm./Kg. body weight), and a Bardic[XX] arterial catheter of suitable size is inserted into the right femoral artery, and connected to the arterial limb of a Helix-reservoir bubble oxygenator (DeWall et al.,[23] 1956), which has been previously assembled and primed with donor blood (McKenzie and Barnard[279] 1958,[280] 1960).

The right atrial appendage is identified (Fig 23 d), an atraumatic silk purse-string suture is placed around its apex, and the ends of the purse-string are threaded through a short cuff of 1/8 inch bore rubber tubing. An auricular clamp is applied below the purse-string, the apex of the appendage is amputated and any obstructing musculi pectinati are cut through (Fig 23 4); as the clamp is released a size 40 Bardic[XX] catheter is inserted into the cavity of the right atrium (Fig. 23 f), and anchored by tightening the purse-string and cross clamping the rubber cuff. The catheter is then connected to the venous well of the oxygenator perfusion is commenced. Because the cavae are not occluded, and the ventricles continue to contract, perfusion is only partial, and blood continues to circulate via the pulmonary bed. During this stage of partial cardio-pulmonary by-pass, intermittent positive-pressure respiration must be maintained.

XX Bardic no. 1055, Manuf. by C.R. Bard. Inc., U.S.A.

FIGURE 23 (a) Resection of the left 5th rib and costal cartilage.

FIGURE 23 (b). Pericardial sac and left phrenic nerve seen from the left.

FIGURE 23 (c). Left atrium and ventricle exposed after incising the pericardium.

FIGURE 23 (d). Right atrial appendage exposed from the left side.

FIGURE 23 (e). Right atrial appendage with apex amputated and purse-string sutures in situ.

FIGURE 23 (f). Right atrial catheter in situ and left atrial appendage just prior to performance of left atriotomy.

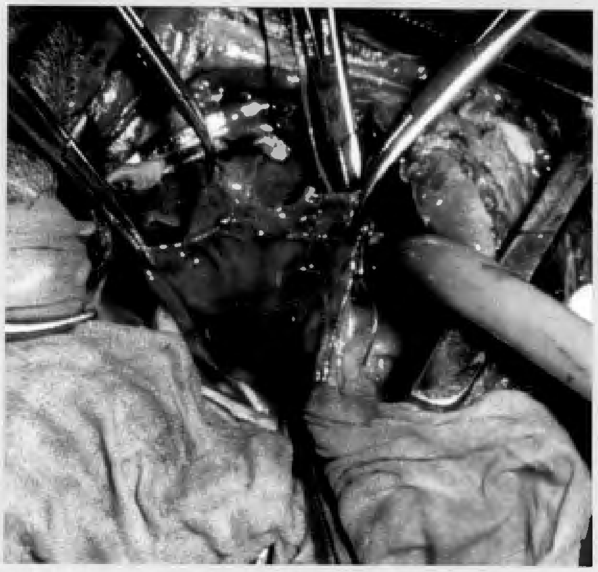


FIGURE 23 (g). Left atrium opened.

FIGURE 23 (h). Horizontal mattress sutures in situ.

FIGURE 23 (i). Prosthesis in situ and sutures tied over a strip of poly-vinyl sponge.

FIGURE 23 (j). Left atrium after closure of atriotomy wound.

Ventricular fibrillation is next induced as described, and once established, respiratory movements are discontinued, the lungs being maintained in a semi-inflated position for the duration of fibrillation. Should the lungs be allowed to collapse, a strong "deflation reflex" is set up(Best and Taylor[227] 1955), with resultant reflex diaphragmatic and mediastinal movements which hinder the surgical manoeuvres.

The lateral wall of the left atrial appendage is then incised in the line of its axis (Fig 23 f), the incision being carried into the wall of the atrium proper, running parallel to the circumflex coronary vessels and terminating just proximal to the entry of the left pulmonary veins (Fig. 23 g). The blood within the left heart, and the bronchial colateral flow which continually empties into the left atrium via the pulmonary veins during total cardio-pulmonary bypass, is aspirated and returned to the oxygenator by means of a cardiotomy sucker.

The postero-lateral mitral leaflet is then identified under direct vision, and excised at its attachment to the annulus fibrosus, the controlling chordae tendineae being severed at their origin from the papillary muscles. A prosthetic valve of suitable size is then fixed to the postero-lateral segment of the annulus by 3 or 4 horizontal mattress sutures (Fig. 23 h). These sutures are preloaded on the prosthesis and passed via the annulus from the ventricular aspect below, to the atrial aspect above, commencing at the postero-medial and working towards the antero-lateral commissure. The prosthesis is then placed within the valve orifice, and the sutures are pulled tight and tied over a strip of compressed poly-vinyl sponge (Fig. 23 i).

The left heart is allowed to fill with blood, all bubbles are evacuated as previously described, and the atriotomy incision is partially repaired in two layers, using a continuous horizontal mattress suture for the first, and a continuous over-and-over suture for the second layer. The patent portion of the atriotomy incision is temporarily clamped, the heart is electrically defibrillated, intermittent positive-pressure respiration is recommenced, and the action of the prosthetic valve and the degree of regurgitation, if any, is assessed by means of a finger inserted into the left atrium. Closure of the left atriotomy is then completed (Fig. 23 j), the perfusion is terminated, and intravenous Protamine Sulphate is administered to neutralise the Heparin. The venous catheter is removed, the defect in the right atrial appendage being closed by tying the purse-string suture which is already in situ, and the chest is closed in layers, a rubber drain connected to a suction apparatus at a negative pressure of -30 mm. Hg. being placed within the pleural cavity. The drain is removed when blood loss from the thorax ceases (usually about 4 hours post-operatively), and the animal is placed in a warmed cage. No special post-operative care, other than anti-biotic therapy, has been administered.

F. <u>The design and testing of prosthetic valves.</u>

A suitable technique for the insertion of prosthetic valves and the prevention of systemic air-embolism having been perfected, various designs of valves were manufactured and tested in hearts set up in the artificial pulse-duplicator, and by insertion into experimental animals. All valves were designed on the principle of a "flap-valve" activated by haemodynamic forces, to be fixed to the postero-lateral segment of the annulus fibrosus, and to project freely into the ventricular cavity below.

<u>Valve 1.</u>

A metal mould (Fig 24) for the production of the first valve (Silastic) which was tested, was manufactured from a scale drawing as previously described. The valve (Fig. 25) consisted of a simple flap, gently concave towards the mitral orifice, and a shoulder, convex towards the mitral annulus to which it was to be sutured; its thickness was such that it would resist eversion during systole by virtue of its strength, and its dimensions were such that it was suitable for insertion into human hearts. By shortening the valve symmetrically from each end, and by trimming the length of the flap as required, the shape of the valve was not significantly altered, and it could be tested by insertion into experimental animals.

On examining the first Silastic valve of this design to be produced, it was immediately apparent that the thickness of the valve was such that while it would tend to resist eversion during systole

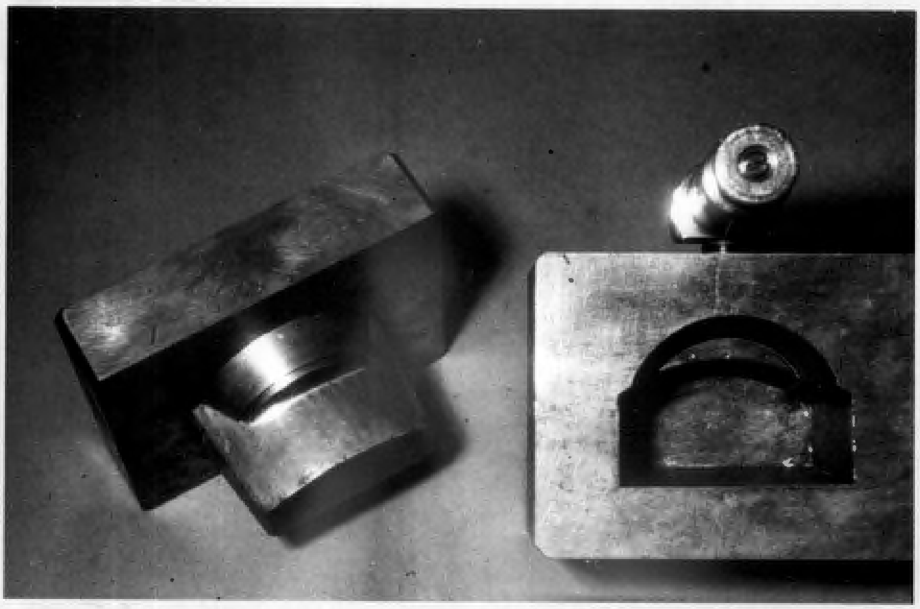


FIGURE 24. Metal mould used for the manufacture of Silastic Valve 1.

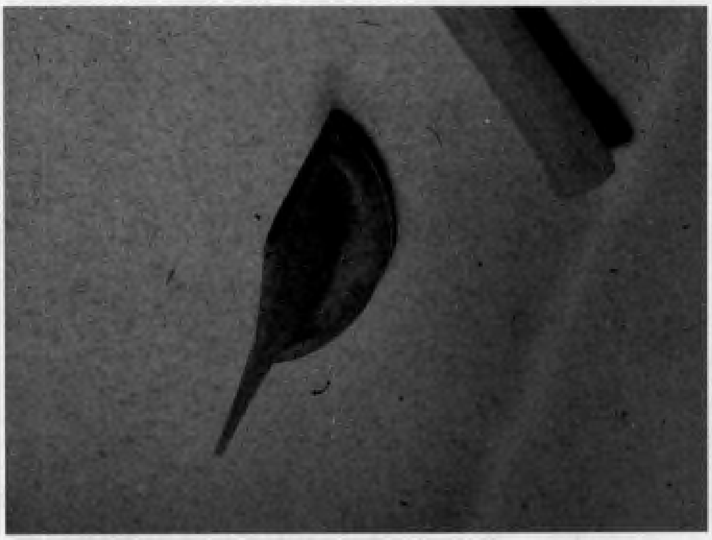


FIGURE 25. Silastic Valve 1 - postero-inferior view.

it resulted in a loss of flexibility and pliability of the flap or cusp. This was clearly an undesirable feature, as in order to ensure tight valve closure, any prosthetic valve and such leaflet tissue as is present in the abnormal valve, must co-apt and become moulded to the contour of one another. Should the leaflets of an incompetent valve be pliable, a relatively rigid prosthesis might suffice, as the leaflets can become moulded to the shape of the latter during closure, but should the leaflets of the abnormal valve be rigid and calcified, such a prosthesis is unlikely to effect a satisfactory closure, even should co-aption occur.

Despite this obvious defect in design, valves of suitable size were sutured to the postero-lateral portion of the mitral annulus of fresh normal human hearts obtained at autopsy and their action studied in the pulse-duplicator (Fig. 26). It was found that the valve did not "flap"as expected, but was forced posteriorly against the ventricular wall. Some degree of competence was achieved however, as the normal aortic cusp closed against the Silastic buttress, but in a diseased heart with an abnormal aortic cusp, such closure would probably not occur.

The action of similar valves was then studied by insertion in experimental animals as described, and the results of previous pulse-duplicator studies were confirmed. On each occasion the valve was forced posteriorly during systole, and failed to control completely the regurgitation caused by excision of the postero-lateral leaflet. In one experiment the prosthesis acted to some extent as a "baffle" against which the normal aortic cusp closed during systole, and

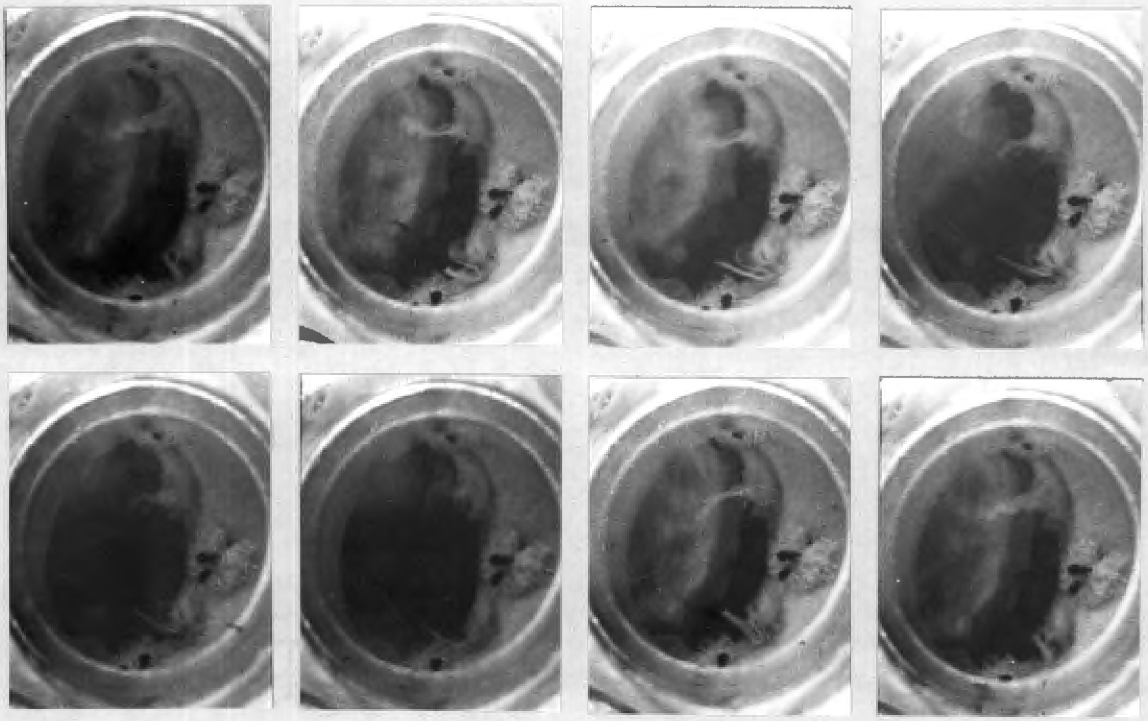


FIGURE 26. Cycle of movements of Silastic Valve 1 showing the opening and subsequent closure.

the animal survived for 50 hours before succumbing to pulmonary oedema. It was concluded therefore that:

(i) The cusp of any Silastic prosthesis, in order to retain its flexibility and pliability and thus act satisfactorily, must be thin.

(ii) As a thin simple Silastic cusp is unlikely to resist the forces acting during systole, without becoming everted into the atrium, and as it is considered inadvisable to construct any form of artificial chordae tendineae, the cusp of the prosthesis must be (a) reinforced in some way, or (b) structurally designed to resist eversion.

(iii) A prosthetic leaflet should be designed with an anterior curvature, so that it projects away from the ventricular myocardium when in the rest position, thus enabling the haemodynamic forces during systole to act upon its posterior surface.

Valve 11.

In an attempt to effect the improvements suggested by a study of Valve 1, a second flap valve which incorporated a thin cusp with an anterior curvature, was designed (Fig. 27). A convex shoulder for purposes of fixation, similar to that of Valve 1, was retained, and in order to prevent the possibility of valve eversion during systole, the cusp was reinforced with a thick central rib or strut. A metal mould of the required design(Fig.17 was manufactured from a scale-drawing (Fig 16) as previously described,

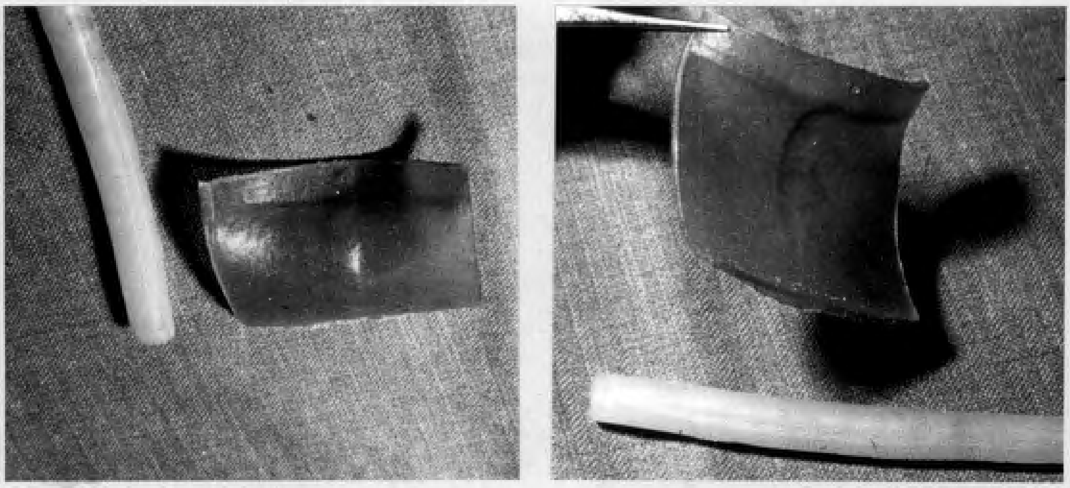


FIGURE 27. Silastic Valve 11 - antero-superior and postero-inferior view.

and the resultant Silastic valves were cut to a suitable size and tested in the artificial pulse duplicator and by insertion in experimental animals.

On examining a Silastic valve of this design, it was noted that the thin cusp was pliable and supple, but that very little force was required to flex the cusp through 180° on the shoulder by which it would be fixed to the annulus. It appeared therefore, that, despite the reinforcing strut, such a valve would be easily displaced posteriorly by the low-pressure influx of blood from the atrium to the ventricle during diastole, and that no stenosis would be caused by its insertion, but that it would be equally easily everted into the atrium during systole, with resultant regurgitation through the valve orifice.

The action of the valve was then studied in hearts set up in the artificial pulse duplicator. At low intraventricular systolic pressures (below 60 m.m. Hg.) the valve functioned as predicted, but as the pressure was progressively increased towards the normal range, the systolic thrust caused the valve to bulge upwards towards the atrium, and a "leak" occured at each "corner" of the valve orifice (Fig. 28). With each beat of the pulse-duplicator the upward bulging became more marked, the regurgitation at each angle of the valve became progressively more severe, and the prosthesis eventually became wedged in the valve orifice with resultant stenosis, or was everted into the atrium with resultant free regurgitation and absolute stenosis.

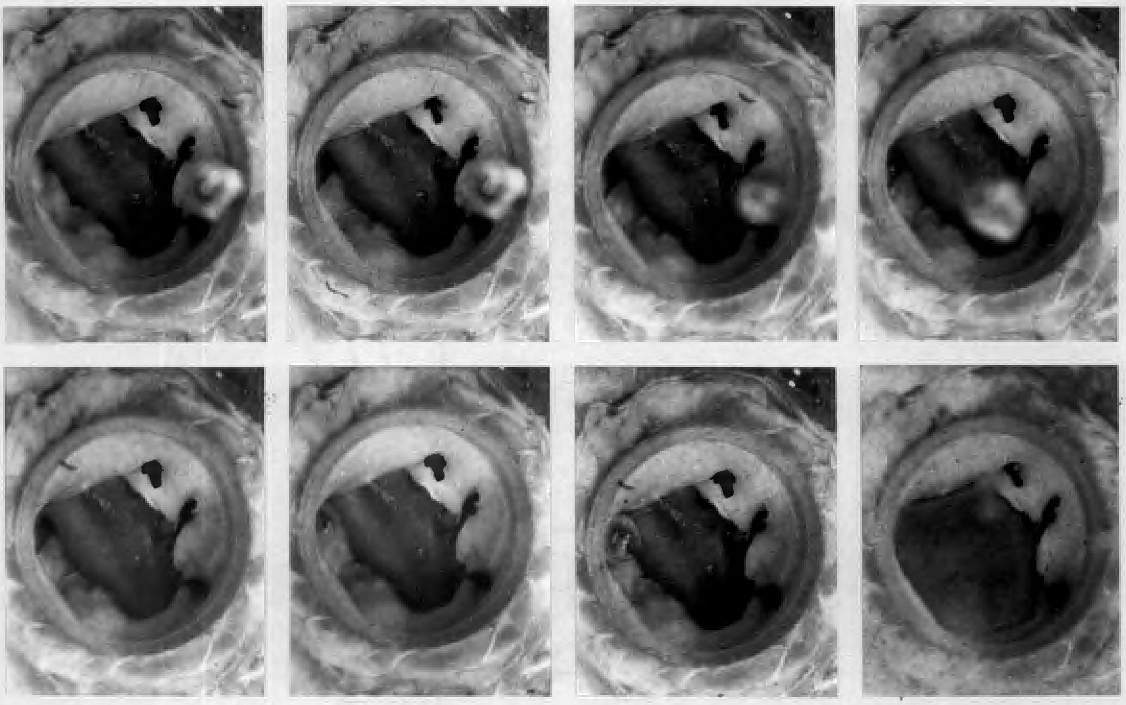


FIGURE 28. Cycle of movements of Silastic Valve 11 showing opening and subsequent closure, with eversion of valve into the atrium. The bubble seen in frames 1-4 is due to a leak at one "corner" of the valve.

In view of the possibility that the systolic sphincter-like action of the mitral annulus might prevent eversion of the prosthetic valve several valves were inserted into experimental animals. On each occasion however the valve became everted as expected and no animal survived the operation.

On the basis of these observations it was concluded that:

(i) A prosthetic valve-cusp with an anterior curvature is satisfactorily activated by the haemodynamic forces active within the left heart chambers,

(ii) The two corners or extremities of any curved flap prosthesis must be sealed off in some way if the valve is to be competent.

(iii) A simple reinforcing strut is inadequate to prevent systolic eversion of a thin Silastic flap, and any prosthesis must be so designed as to resist eversion by virtue of its structural shape.

<u>Valve 111</u>.

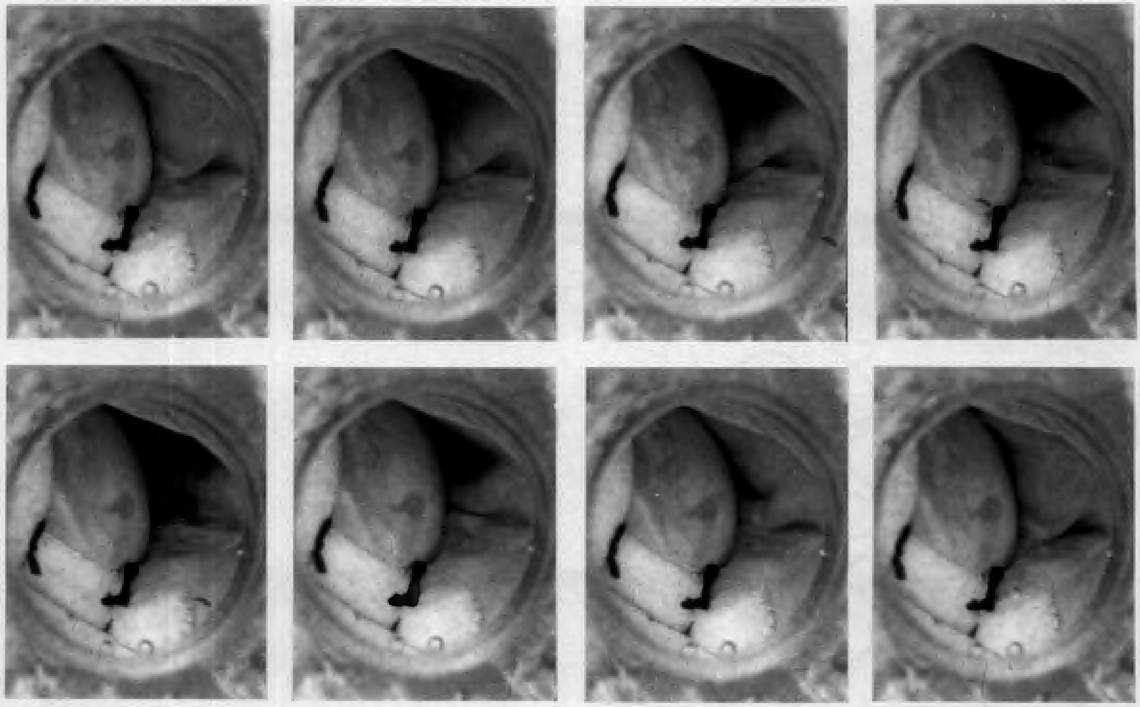
At this stage it became obvious that it was impractical to continue making Silastic valves for experimental work, and the technique of manufacturing latex-rubber valves which has been described, was devised, Using this technique (Fig, 18) several valves of varying size and thickness were constructed on the principle of an "inverted cup" (Fig. 29). Each consisted of a shoulder, convex towards the annulus to which the valve was

FIGURE 29. Photograph of Valve 111 - posterior (middle valve) and anterior views of 3 different sized valves.

to be fixed, and from which a cusp with an anterior curvature and convex from side to side, projected. It was thought that such a valve would billow up during systole, thus occluding the incompetent orifice, and that the resultant increase in size of the cup would obviate the possibility of its being everted through the valve orifice. The convexity of the cusp in all planes was thought to be an additional factor which would resist eversion, and because of the closed cup-shape of that portion of the prosthesis which would occupy the valve orifice, regurgitation at the angles of the valve, as occurred with Valvell, appeared unlikely.

On examining valves of this design, it was noted that the convex leaflet and general cup shape added considerably to their strength, and it appeared that a valve of reasonable thickness was unlikely to be everted during systole. Only extremely thin valves however appeared likely to billow under the influence of the pressures acting during systole.

Valve action was then studied in the artificial pulse-duplicator as before (Fig. 30). It was found that very thin valves billowed during systole as expected, but after a few beats of the pulse-duplicator they became everted into the atrium. Valves of a reasonable thickness on the other hand, while showing little or no billowing, did not become everted into the atrium, and completely controlled regurgitation through the valve orifice. The cusps of such valves however underwent very little excursion during the pulse-duplicator cycle, and in fact these valves did not function as mobile prostheses. Their ability to prevent regurgitation



<u>FIGURE 30</u>. Cycle of movements of Valve 111 showing opening and subsequent closure.

was mainly dependent upon the bulk of each acting as a baffle, against which the normal aortic leaflet closed during systole, and this very bulk, of necessity resulted in an intolerable degree of stenosis of the orifice. Regurgitation at each angle of the valve orifice, as occured with Valve 11 was not observed, and this appeared to be due to the cup-shape of the prosthesis.

Several valves were then inserted into experimental animals and the failure of the cup to billow during systole was confirmed. It was observed that the whole valve tended to rotate anteriorly on the annulus during systole, so that in the experimental animal the valve cusp did in fact undergo some excursion. Despite this rotation however the valve was not everted into the qtrium, and this appeared to be due in part to the prosthetic cusp striking the aortic leaflet and being restrained thereby. Regurgitation caused by excision of the normal mural leaflet was always controlled, and no "leak" occured at the angles of the valve orifice, but because of the bulk of the prosthesis, masked mitral stenosis with resultant acute pulmonary oedema was produced, and no animal survived the operation.

The above study indicated:

(i) That a cup-shaped prosthesis is able to prevent regurgitation through the angles of the valve orifice.

(ii) That a prosthetic valve whose competence depends upon its billowing during systole must be thin.

(iii) That eversion of the cusp of a cup-shaped prosthesis tends to be resisted by virtue of its structural shape, but that such structural shape alone is insufficienct to prevent eversion. A combination of structure and strength is therefore necessary to prevent eversion of any flap-type prosthesis which is not anchored inferiorly.

(iv) That the presence of the aortic leaflet of the mitral valve, by acting as a baffle against which the prosthetic cusp may abut during systole, plays a part in preventing eversion of a flap-type valve. A diseased rigid cusp, would probably act as an even more effective barrier to restrain such a prosthesis.

(v) That a cup-shaped valve to be of value, must be modified in some way to allow a free flow of blood from the atrium to the ventricle during diastole.

Valve lV.

In an attempt to relieve the stenosing effect of Valve lll, the design was modified by saucering the anterior aspect of the valve cusp (Fig. 31). The saucered area was designed to be thin enough to billow during systole, and the lateral portions of the valve were thickened in order to resist systolic eversion. It was thought that during systole the cusp of the valve would flap, and the saucered area billow, thus controlling regurgitation, but that it would revert to its rest position during diastole thus allowing of a free flow of blood from the atrium into the ventricle.

Latex-rubber valves of the above design were then manufactured, and on examination it became obvious that by saucering the cusp a structural

FIGURE 31. Photograph of Valve 1V - posterior and anterior views.

weakness had been introduced. Slight pressure on the posterior aspect of the cusp caused it to become flexed anteriorly as though it were attached to the cup portion of the valve by a hinge. This tendency to flexion could not be counteracted by thickening the cusp or by reinforcing the lateral portions of the valve, and it appeared that the haemodynamic forces acting during systole would have a similar effect. The possibility nevertheless existed that systolic billowing of the saucered area would prevent the tendency to flexion, and valves were therefore tested in the artificial pulse-duplicator

Pulse-duplicator studies (Fig. 32) revealed that a valve of this design did not flap or billow as expected, but that the cusp was forced posteriorly against the ventricular myocardium, and acted simply as a baffle as had previously been observed during a study of Valve 1.

Regurgitation through the angles of the valve orifice was not observed but there was nothing to suggest that in the presence of a normal aortic leaflet a simple baffle of similar size would not have brought about the same degree of correction. Because of the modification of saucering, the square area of the prosthesis occupying the valve orifice was considerably less than that of Valve 111, and no stenosis was produced (Fig. 32). Valves of suitable size were then inserted into experimental animals and the above observations were confirmed. On no occasion did the prosthesis function as a flap valve, and flexion of the cusp at the structurally weak area did not occur. Such competence as was achieved appeared to be due to the bulk of the prosthesis and the action of the normal septal leaflet, and billowing of the cusp played no

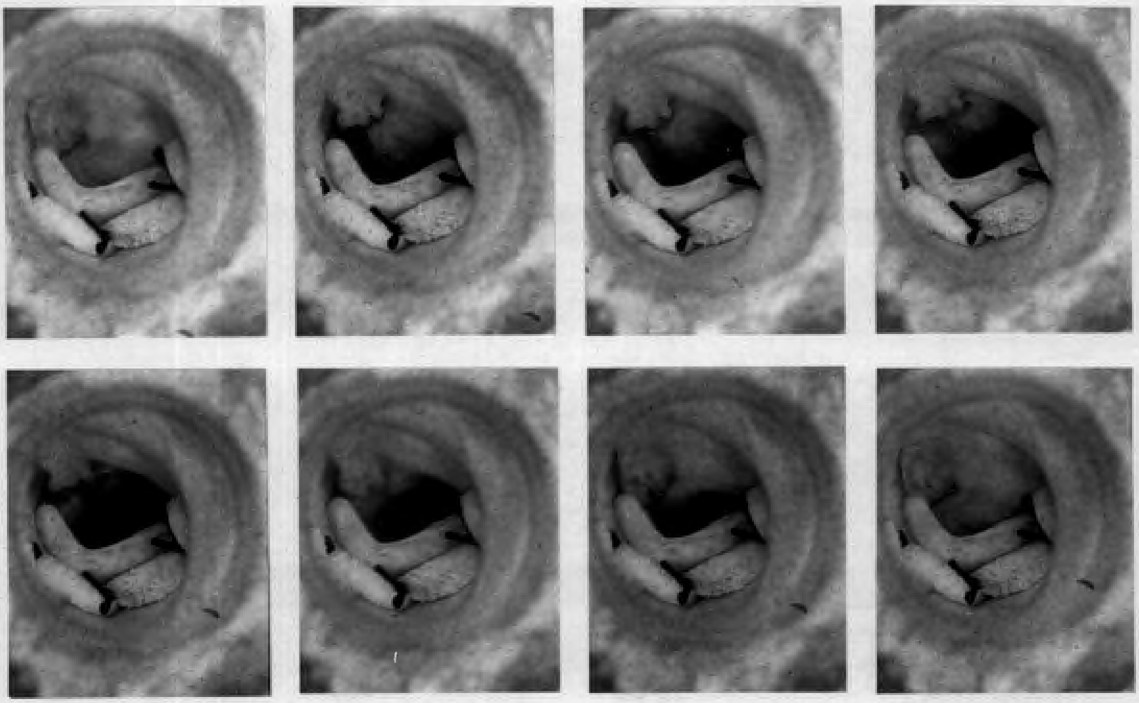


FIGURE 32. Cycle of movements of Valve 1V showing opening and subsequent closure.

part in the control of regurgitation.

As it was obvious that the design of Valve 1V was unsatisfactory, and as the survival of any animal with such a prosthesis in place could serve no useful purpose, each experiment was abandoned after the action of the valve had been thoroughly studied.

The above experiments confirmed:

(i) That in order to be satisfactorily activated during systole a prosthetic leaflet should be designed with an anterior curvature.

(ii) That any prosthesis which occupies but a small segment of the total valve-orifice surface-area during diastole, does not cause stenosis.

<u>Valve V.</u>

In a further attempt to relieve the stenosing effect of Valve 111, a latex-rubber valve with a central anteriorly curved strut, and two thin lateral receding flaps, was manufactured (Fig. 33). The lateral margins of the two flaps were thickened to add to the strength of the valve and a convex shoulder for the purpose of fixation, similar to that of Valve 111, was retained. It was thought that this complex valve cusp would both flap and billow under the influence of the haemodynamic forces acting during systole, thus controlling regurgitation, but that it would revert to its rest position during diastole, and that the small area of the prosthesis (T-shaped when viewed from above) which occupied the valve orifice, would not cause stenosis.

On examination Valve V appeared to possess some measure of strength by virtue of its design, but it was necessary to reinforce

FIGURE 33. Valve V - superior, anterior, and posterior views.

its central rib and lateral margins before its strength appeared to be such that it would resist systolic eversion. It was found that slight pressure on the posterior surface of the cusp caused it to flap as expected, but in addition the lateral flaps billowed due to the structural design of the valve. This effect is advantageous in that during life, as the intraventricular pressure begins to rise and the cusp as a whole is activated, the lateral flaps immediately billow, and the incompetent orifice is sealed off early in systole. Later in the cycle as systole progresses, and the intraventricular pressure rises to a maximum, the flaps are distended directly by the haemodynamic pressure acting upon their posterior surface.

Latex valves of this design were then fixed in fresh human hearts obtained at autopsy, and their action studied in the artificial pulse-duplicator (Fig. 34). It was found that the valves functioned as predicted that regurgitation caused by excision of the postero-lateral leaflet was completely controlled, and that the intraventricular pressure could be raised to a level considerably higher than that to be expected during life, without causing eversion of the prosthesis. The surface area of that portion of the prosthesis occupying the valve orifice during systole was greater than one-half the total area of the valve orifice, and it appeared that such a device would adequately compensate for a deficiency of leaflet tissue of the degree which is commonly encountered in patients suffering from mitral insufficiency.

Similar valves of suitable size were then inserted into 6 dogs and were found to function as described and to control free regurgitation

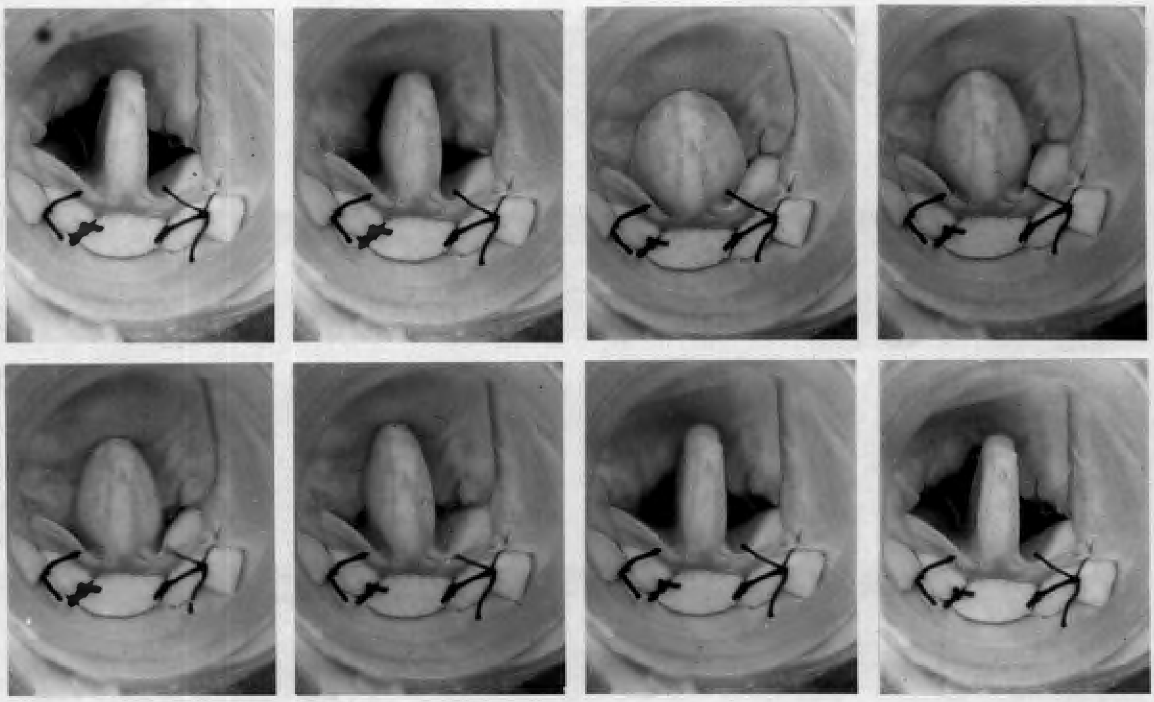


FIGURE 34. Cycle of movements of Valve V showing closure and subsequent opening.

caused by excision of the postero-lateral cusp. No thrill was palpable over the left atrium after valve insertion, and post-operatively no systolic murmur was audible on ausculation. Pressure studies at operation confirmed that the prosthesis did not obstruct the valve orifice. All animals regained conciousness after the operation, were able to eat and stand and survived normally for from 12 - 24 hours. At this stage the latex valves, which are weak and unable to withstand the stresses to which they were subjected, ruptured, and the animals succumbed to the effects of the sudden free mitral regurgitation. This was confirmed by post-mortem examination, which in every case, showed that the valve flaps had ruptured (Fig. 35) and that the animal had died of acute pulmonary oedema.

Once it had been established, by pulse-duplicator studies and animal experiments, that Valve V was mechanically effective the manufacture of a mould for the production of Silastic valves of similar design was commenced. A white-metal model (Fig. 36) - a copy of a plaster-of-paris block mould - was machined, and by painting the metal model with several layers of liquid latex, pliable latex valves were produced. These were studied in the pulse-duplicator as before, and alterations to the white-metal mould were effected as indicated, until the action of latex valves produced, was found to be satisfactory. The metal mould was then used as a "pattern" for the manufacture of a 3 - piece aluminium mould for the production of Silastic valves (Fig. 37).

The different physical properties of Silastic and Latex already mentioned, are such that it was realised that the ideal thickness of the

FIGURE 35. Photograph of Valve V (latex-rubber) fixed to the postero-lateral segment of the mitral ring, in a heart removed from a dog at autopsy 20 hours post-operatively. Note the ruptured flap of the valve.

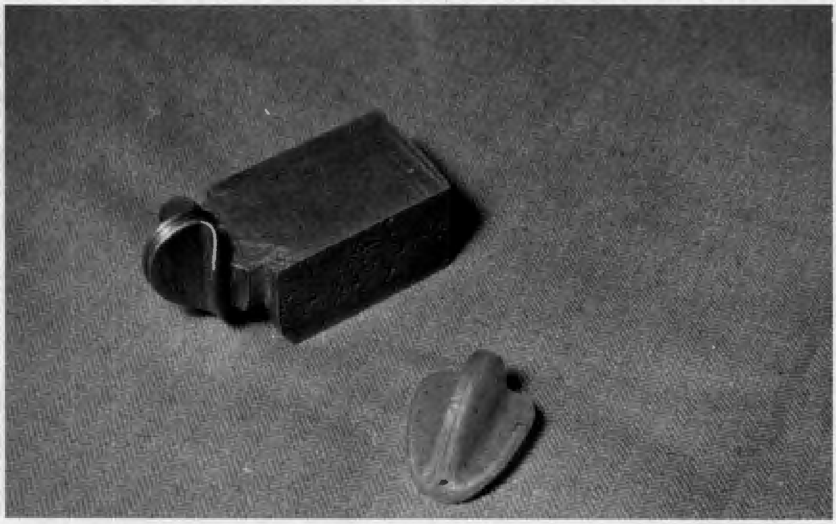


FIGURE 36. White-metal "positive" mould of Valve V and a latex-rubber valve manufactured on this mould.

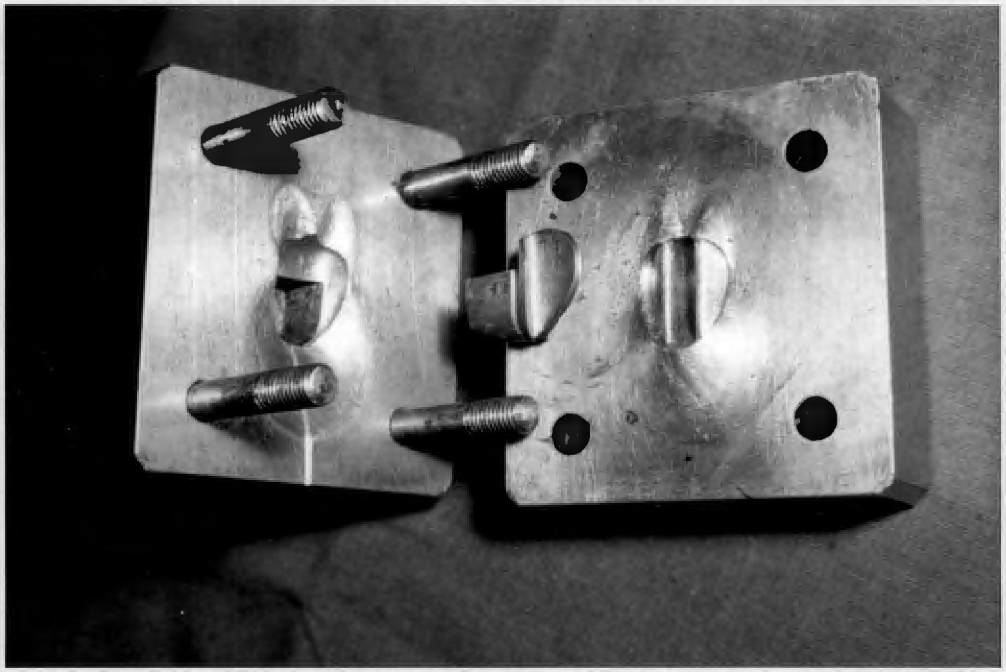


FIGURE 37. Three piece metal mould used for the manufacture of Silastic Valve V.

various portions of the Silastic valve would have to be determined by trial and error. Major alterations to this complex 3-piece mould obviously would not be possible, and it was therefore decided to design the first mould to produce thin valves, which could be thickened or reinforced as indicated, by minor alterations to the "female" component of the mould.

The first Silastic valve was then manufactured and heat cured as described, and subjected to tests in the pulse-duplicator. Alterations to the mould were effected as indicated until pulse-duplicator studies showed that the action of the Silastic valves closely resembled that of the Latex valves previously studied. Several acute animal experiments were then performed, and the satisfactory mechanical action of the Silastic valves and their ability to control regurgitation without the production of stenosis, was confirmed.

Prior to the performance of survival studies in experimental animals it was necessary to confirm that there Silastic valves were durable. A valve was therefore sutured to one half of the circumference of an oval hole of suitable size cut in a piece of compressed polyvinyl sponge, and set up in the pulse-duplicator chamber as previously described. The apparatus was switched on, regulated so as to subject the valve to 160 flexions per minute, at a systolic pressure of 200 mms. Hg., and allowed to run for 30 days. Examination of the valve at the end of this period, during which time it had undergone 115,000 flexions, failed to reveal any signs of wear.

It was thus apparent that a Silastic valve of this design would last for at least 3 months (and in the light of Barnard's [274] (1958) previous experiments, probably considerably longer) in a dog, with an average heart rate of 100 beats per minute and a systolic pressure of approximately 100 mms. Hg., and this period was considered to be sufficient to enable one to study the effects of the prosthesis on the blood in vivo.

The many alterations to the aluminium mould, which had been necessary to establish the optimal dimensions of the various parts of the valve resulted in the surfaces of the final Silastic valves being rough and irregular and these valves were unsuitable for in vivo experiments. A second highly polished mould of identical size and shape was therefore made, and the smooth, regular valves produced were inserted into experimental animals, and their effects on the blood and circulation studied.

In 3 initial experiments, mattress sutures were pre-loaded on the prosthesis, passed via the annulus, and tied over a strip of compressed polyvinyl sponge as previously described. All 3 animals recovered normally from the operation and progressed satisfactorily for the first 2 days, only to succumb between 48 - 72 hours post-operatively to the effects of acute pulmonary oedema. At autopsy in each case it was found that one or more of the sutures had cut through the Silastic shoulder by which the prosthesis was anchored to the annulus, with resultant regurgitation of blood between the prosthesis and the annulus. In the remaining experiments therefore, a strip of compressed polyvinyl sponge was fixed to the inner aspect of the posterior shoulder of the valve, to prevent the sutures cutting through.

The size of the only Silastic prosthesis available was such that it was satisfactory for the control of regurgitation in the average 20 Kg. dog. On 2 occasions however, it was found at operation that the valve was too small and the experiment had to be abandoned. In 2 other experiments the prosthesis failed to control regurgitation caused by excision of the postero-lateral leaflet and the animals died of acute pulmonary oedema a few hours post-operatively; autopsy revealed that both valves had been incorrectly placed.

In all the remaining experiments the prosthesis controlled the induced regurgitation without causing stenosis. One dog survived normally for 16 days and on examination showed no signs of mitral insufficiency. On the 16th post-operative day shortly after having been exercised, it was noticed that the animal's hind-quarters were paralysed; the animal was therefore sacrificed and at autopsy it was found that intra-cardiac clotting had occured (Fig. 38) and that a portion of the clot had broken off to form a peripheral embolis. Several animals survived for 6 - 8 days. Embolism, with resultant paralysis of the hind-quarters then occured, the animals were sacrificed and at post-mortem examination intra-cardiac thrombosis of similar distribution was demonstrated. No animal survived for longer than 48 hours without showing some degree of thrombosis at autopsy.

This regular occurence of intra-cardiac thrombosis in experimental animals demonstrates that Silastic Valve V, though mechanically efficient durable, and easy to insert in the desired position within the heart, is not yet suitable for clinical application. If the problem of clotting can be overcome, a valve of this design will satisfactorily control regurgitation

FIGURE 38 a. Photograph showing thrombus in relation to Silastic Valve V, in a heart removed from a dog at autopsy 16 days post-operatively (antero-superior view).

FIGURE 38 b. Photograph showing thrombus in relation to Silastic Valve V, in a heart removed from a dog at autopsy 16 days post-operatively (postero-inferior view).

due to an absolute deficiency of leaflet tissue, and clinical trial will be instituted.

CONCLUSIONS.

1. The surgical correction of the incompetent mitral valve must be performed under direct vision employing some form of mechanical pump oxygenator. The actual operative technique to be employed in each case, can be determined only after inspection of the action and pathological anatomy of the diseased valve at operation. Perforated or cleft leaflets may be repaired by simple suture; leaflet mobility may be restored by separation of fused commissures, removal of calcium from the leaflets or separation of abnormal chordo-papillary adhesions; and dilatation of the annulus fibrosus may be corrected by annuloplasty. The control of regurgitation due to an absolute deficiency of the leaflet tissue may be effected by an immobile compressed poly-vinyl sponge (Ivalon) baffle, but in those cases where a baffle of suitable size is found to cause stenosis, the restoration of complete competence can only be achieved by means of a mobile prosthetic valve.

2. The anatomy of the normal mitral valve is such, that any form of prosthesis can be most safely and securely fixed to the postero-lateral portion of the valve ring - interference with the root of the aorta, the leaflets of the aortic valve or the left-ventricular outflow-tract is thus avoided.

3. The leaflets of the normal mitral valve are activated by a differential hydrostatic pressure and restrained by the anchoring chordae tendineae and papillary muscles, and efficient leaflet action is facilitated by the sphincteric action of the valve ring. A flap-type prosthetic valve, fixed to the postero-lateral sector of the mitral annulus, can be designed to be similarly activated, and does not interfere with the sphincter action of the valve ring. As the anatomy and mechanism of action of the chordo-papillary system is too complex to be imitated surgically, such a prosthesis must be designed to resist systolic eversion by virtue of its strength or structural shape.

4. Silastic-a pliable, durable, inert silicone-rubber compound - is more suitable than tissue grafts for the fabrication of prostheses, grafts having been shown to undergo fibrosis and shrinking after a short period. The use of Latex-rubber prostheses, which may be rapidly and inexpensively manufactured and modified as indicated, greatly simplifies the study of valve design.

5. A direct vision left thoracic approach to the mitral valve is satisfactory for animal experiments. Systemic air embolism, a recognised complication of open left-atriotomy may be prevented by the use of elective ventricular fibrillation.

6. The Silastic flap-type valve, activated by haemo-dynamic forces and fixed to the postero-lateral portion of the mitral annulus, which has been designed (Valve V) is mechanically efficient, durable, and easy to insert in the desired position within the heart. The regular occurrence of intra-cardiac thrombosis in experimental animals however, renders this valve unsuitable for clinical application at the present time. If the problem of clotting can be overcome, such a valve will satisfactorily control regurgitation due to an absolute deficiency of leaflet tissue, and will be used clinically for the correction of mitral insufficiency in suitable cases.

SUMMARY.

1. Despite the remarkable advances in cardiac surgery during recent years, suitable techniques for the correction of all pathological types of mitral insufficiency have not yet been established. In many cases, complete correction can be effected by relatively simple surgical techniques, but the complete solution to this problem awaits the developement of a suitable mobile prosthesis.

2. A detailed post-mortem study of the anatomy of the normal valve and the pathological anatomy of the incompetent valve was carried out, and valve action was studied at open operation and by means of an artificeal pulse-duplicator, designed for the purpose. As a result of these studies it was decided to design and test a simple flap type valve, which would be fixed to the postero-lateral sector of the mitral annulus fibrosus. Such a valve should not interfere with the complex relationships of the antero-medial portion of the mitral annulus, or the normal sphincter-like action of the valve ring, and should be activated by the haemo-dynamic forces normally active within the chambers of the heart.

3. The use of intra-cardiac tissue grafts having been shown by numerous previous workers to be unsatisfactory, it was decided to use an artificial material for the fabrication of the prosthesis. Silastic -

a pliable, durable, inert silicone-rubber compound - was found to be the most satisfactory artificial substance available. The fabrication of Silastic valves soon proved to be costly and time-consuming and a technique for the fabrication of Latex-rubber valves for preliminary experiments was therefore devised.

4. A suitable technique for the insertion of valves in experimental animals was devised. All operations were performed under direct vision using the Helix-reservoir bubble oxygenator. A direct left-sided approach to the mitral valve was found to be superior to a right thoracotomy approach in the normal dog. The use of elective ventricular fibrillation was found to be a safe and reliable technique for the prevention of systemic air embolism, a recognised complication of open left atriotomy.

5. Silastic and Latex-rubber flap type valves were designed and manufactured, and their action studied in hearts set up in the artificial pulse-duplicator and in experimental animals. Defects in valve design were detected and modifications effected as indicated until a mechanically efficient Silastic valve was developed. Prolonged action in the pulse-duplicator proved that such a valve was durable, and experimental operations on dogs confirmed that the valve was easy to insert in the desired position within the heart. All these animals however developed intra-cardiac thrombosis within

6 - 16 days of the operation.

6. It is concluded that a Silastic flap valve (Valve V) sutured to the postero-lateral portion of the mitral annulus fibrosus, although mechanically efficient, durable, and easy to insert in the desired position within the heart, is at present unsuitable for clinical use as it causes intra-cardiac clot formation. If this complication can be prevented such a valve may be employed clinically for the correction of those pathological types of mitral insufficiency, which are not able to be corrected by surgical techniques at present available.

REFERENCES

1. SHERMAN, H.M. "Suture of Heart Wounds". J. Amer. Med. Ass. 38:1560, 1902.

2. BAILEY, C.P. "The Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy). Dis. Chest. 15:377, 1949.

3. BAKER, C., BROCK, R.C., and CAMBELL, M. "Valvulotomy for Mitral Stenosis; Report of Six Successful Cases". Brit.Med. J. 1:1283, 1950.

4. O'SHAUGHNESSY, L. "Future of Cardiac Surgery". Lancet. 2:969, 1939.

5. BIGELOW, W.G., LINDSAY, W.K., GREENWOOD, W.F. "Hypothermia - its possible role in Cardiac Surgery". Ann. Surg. 132:849, 1950.

6. BIGELOW, W.G., CALLAGHAN, J.C., HOPPS, J.A. "General hypothermia for experimental intra-cardiac surgery". Ann. Surg. 132:531, 1950.

7. BOEREMA, I.A., WILDSCHUT, A., SCHMIDT, W.J.H., and BROCKHUYSEN, L. "Experimental researches into hypothermia as aid in surgery of the heart; preliminary communication". Arch. Chir. Nederl. 3:25, 1951.

8. DELORME, E.J. "Experimental cooling of the blood-stream". Lancet. 2:914, 1952.

9. ROSS, D.N. "Hypothermia" Guys Hosp. Rep. 103:97, 1954.

10. LYNN, R.B.,MELROSE, D.G., CHURCHILL-DAVISON, H.C., and MACMILLAN, I.K.R. "Hypothermia - further observations on surface cooling". Ann. Roy. Coll. Surg. Eng. 14:267, 1954.

11. GRAY, T.C. "Induced Hypothermia" Proc. Roy. Soc. Med. 48:1083, 1955.

12. SWAN, M., BLOUNT, S.G. "Visual Intracardiac Surgery in a Series of one hundred and eleven Patients". J. Amer. Med. Ass. 162:941, 1956.

13. BAILEY, C.P. Discussion on paper by LEWIS, F.J., SHUMWAY, N.E., NIAZI, S.A., and BENJAMIN, R.B. "Aortic valvulotomy under direct vision during hypothermia". J. Thor. Surg. 32:496, 1952.

14. BJORK, V.O. "An artificial heart or cardio-pulmonary machine". Lancet. 2:491, 1948.

15. GIBBON, J.H. "The maintenance of life during experimental occlusion of the pulmonary artery, followed by survival". Surg. Gynae. Obst. 69:602, 1959.

16. GIBBON, J.H. MILLER, B.J., DOBELL, A.R., ENGELL, H.C., VOIGT, G.B. "Closure of interventricular septal defects in dogs during open cardiotomy with the maintenance of the cardio respiratory functions by a pump-oxygenator". J. Thor. Surg. 28:235, 1954.

17. JONGBLOED, J. "The mechanical heart-lung system". Surg. Gynae. Obst. 89:684, 1949.

18. DENNIS, C., KARLSON, K.E. EDER, W.P., NELSON, R.M., EDDY, F.B., SANDERSON, D. "Pump oxygenator to supplement the heart and lungs for brief periods". Surgery. 29:697, 1951.

19. MELROSE, D.G. "A mechanical heart-lung for use in man" Brit. Med. J. 2:57, 1953.

20. DODRILL, F.A., HILL, E., GERISCH, R.A., JOHNSON, A. "Pulmonary valvuloplasty under direct vision using the mechanical heart for a complete by-pass of the right heart in a patient with congenital pulmonary stenosis". J. Thor. Surg., 26:584, 1953.

21. MUSTARD, W.T., CHUTE, A.L., KEITH, J.D., SIREK, A., ROWE, R.D., VLAD, P. "A surgical approach to transposition of the great vessels with extra-corporeal circuit". Surgery. 36:39, 1954.

22. LILLEHEI, C.W., DEWALL, R.A., READ, R.C., WARDEN, H.E., VARCO, R. "Direct vision intra-cardiac surgery in man using a simple disposable artificial oxygenator". Dis. Chest. 29:1, 1956.

23. DEWALL, R.A., WARDEN, H.E., READ, R.C., GOTT, W.L., ZIEGLER, N., VARCO, R.L., LILLEHEI, C.W. "A simple expendable Artificial Oxygenator for open heart surgery". Surg. Clin. N. Amer. 36:1025, 1956.

24. KIRKLIN, J.W., DONALD, D.E., HARSHBARGER, H.G., HETZEL, P.S., PATRICK, R.T. SWAN, H.J.G., WOOD, E.H. "Studies in extra-corporeal circulation. Applicability of Gibbon-type pump-oxygenator to human intra-cardiac surgery; 40 cases". Ann. Surg. 144:2, 1956.

25. KOLFF, W.J., EFFLER, D.B., GROVES, L.K., PEEREBOOM, C., MORACA, P.P. "Disposable membrane oxygenator (heart-lung machine) and its use in experimental surgery". Clev. Clin. Quart. 23:69, 1956.

26. CHURCHILL, SIR W.S. Quoted by GUTHRIE, D. "A History of Medicine". Thomas Nelson and Sons. Ltd. London. 1945.

27. QUAIN. "Elements of Anatomy". Vol. 1V. Part 3. The Heart. 11th ed. Longmans, Green, and Co. London. 1929.

28. REHN, L. "Ueber penetrierende Herzwunden und Herznaht" Arch. f. Klin. Chir. 60:315, 1897.

29. HIPPOCRATES. "The genuine works of Hippocrates". Aphorisms V1. 18. Translated by Francis Adams, New York. William Wood and Co.

30. BALLANCE, SIR CHARLES. "The Surgery of the Heart". Lancet. 1:1, 1920.

31. ARISTOTLE. Cited by LOCKWOOD, A.L. "Surgery of the Pericardium and Heart". Arch. Surg. 18:417, 1929.

32. GALEN. Cited by LOCKWOOD, A.L. Ref 31. Arch. Surg. 18:417, 1929

33. FALLOPIUS. Cited by LOCKWOOD, A.L. Ref 31. Arch. Surg. 18:417, 1929.

34. BOERHAAVE. "De vulnese in genese, aphorismi de cognoscendis et curandis morbis". Aphorism 170. Cited by LOCKWOOD, A.L. Ref. 31. Arch. Surg. 18:417, 1929.

35. HOLLERIUS. Cited by FISCHER, G. Ref. 41. Arch. f. Klin. Chir. 9:571, 1868.

36. CABRIOLANUS. cited by SIR CHARLES BALLANCE. Ref 36. Lancet. 1:1, 1920.

37. TOURBY. cited by SIR CHARLES BALLANCE. Ref. 36. Lancet. 1:1, 1920.

38. MORGAGNI. "De sedibus et Causis Morborum". cited by LOCKWOOD, A.L. Arch. Surg. 18:417, 1929.

39. ROMERO. "The Surgery of the Heart". cited by PAGET, S. 1897.

40. LARREY, BARON D.J. cited by SIR CHARLES BALLANCE. Ref. 36. Lancet. 1:1, 1920.

41. FISCHER, G. "Die Wunden des Herzens und des Herzbeutels". Arch. f. Klin. Chir. 9:571, 1868.

42. MORTON, WILLIAM T.G. "Letters from Dr. W.T.G. Morton". Amer. J. Dent. Sci. 8;56, 1847.

43. LISTER, J. "A new method of treating compound fracture, abscess etc". Lancet. 2:95, 353, 668, 1867.

44. PASTEUR, LOUIS. cited by GARRISON, F.H. "An Introduction to the History of Medicine". W.B. Saunders Co., Philadelphia. 1929.

45. BECKER, O. "Ueber die Sichtbaren Erscheinungen der Blutbewegune in der Menschlichen Netzhaut". Arch. f. Opthalmologie. 18:206, 1872.

46. KLEBS, E. "Ueber Operative Verletsungen der Herzhlappen und deren Folgen" Prag. Med. Wochenscher. 1:29, 1876.

47. COHNHEIM, J. "Vorlesunger uber Allgemeine Pathalogie" Berlin, Hirschwald. 1:38, 1877.

48. TIMOFEJEW, A. "Zur Frage ueber die Insufficienz der Semilunarklappen der Aorta". Berl. Klin. Wchnschr. 25:477, 1888.

49. ROSENBACH, O. "Ueber der Mechanismus des Aortenhlappenschlusses". Berl. Klin. Wchnschr. 26:26, 1889.

50. BLOCK, M.H. "Ueber Wunden des Herzens und ihre Heilung Durch die Naht unter Blutleere". Deutsche Gesellsch. f. Chir. 11:108, 1882.

51. REED, R. quoted by McGuire, D.L. "A successful Surg. Gynae. Obst. 40:623, 1925.

52. DALTON, H.C. "Report of a case of stab-wound of the pericardium". Ann. Surg. 21:;47, 1895.

53. DEL VECCHIO. "Suturo del cuore" Riforma Med. 2:38, 1895.

54. BILLROTH. quoted by ROSE, E. "Hertzamponade" Deutsche Ztschr. f. Chir. 20:329, 1884.

55. BILLROTH. quoted by JEGER, E. "Die chirurgie der Blutgefasse und der Herzens". Berlin. 1913.

56. RIEDINGER quoted by LOCKWOOD, A.L. Ref. 31. Arch. Surg. 18:417, 1929.

57. PAGET, S. "The Surgery of the Chest". John Wright and Co., London. 1896.

58. WEILL, E. "Traitědes maladies du coeur chez les enfants". Paris 1895.

59. DELORME, E. cited by KING, E. "Surgery of the Heart" Edward Arnold and Co., London. 1941.

60. TUFFIER, T. et HALLION, J. "De la compression rythmée du coeur la syncope cardiagué par embolie". Bull. et Mém. Soc. de Chir. 24:937, 1898.

61. SAMWAYS, D.W. "Cardiac Peristalsis". Lancet. 1:927, 1898.

62. BRUNTON, SIR LAUDER. "Preliminary note on the Possibility of Treating Mitral Stenosis by Surgical Methods". Lancet 1:392, 1902.

63. MacCULLUM, W.G. and McCLURE, R.D. "On the mechanical effect of experimental mitral stenosis andinsufficiency". Bull. Johns Hopkins Hosp. 17:260, 1906.

64. WIGGERS, C.J. anddu BOIS, E.F. "Methods for the production of Temporary Valvular Lesions". Proc. Exper. Biol. and Med. 10:87, 1913

65. HAECKER, R. "Experimentelle Studien zur Pathologie und Chirurgie des Herzens". Arch. f. Klin. Chir. 84:1035, 1907.

66. CUSHING, H. and BRANCH, J.R.B. "Experimental and clinical notes on Chronic Valvular Lesions in the Dog. and their possible relation to a future surgery of the Cardiac Valves". J.M. Res. N.S. 12:471, 1907.

67. JEGER, E. "Die Chirurgie der Blutgefässe und der Herzens". Berlin. 1913.

68. DOYEN, E. "Chirurgie des malformation congenitales au acquisis du couer". Presse Méd. 21:860, 1913.

69. TUFFIER, T. "Etat actuel de la chirurgie intrathoracique". Trans. Internat. Cong. Med. P. 247. Sec. 7. London. 1913.

70. CUTLER, E.C., LEVINE, S.A. and BECK, C.S. "The Surgical Treatment of Mitral Stenosis:Experimental and clinical Studies". Arch. Surg. 9:689, 1924.

71. CUTLER, E.C., and LEVINE, S.A. "The present status of the surgical procedures in chronic valvular disease of the heart". Arch. Surg. 18:403, 1929.

72. ALLEN, D.S., and GRAHAM, E.A. "Intracardiac Surgery - A New Method". J. Amer. Med. Ass. 79:1028, 1922.

73. SOUTTAR, SIR HENRY. "The Surgical Treatment of Mitral Stenosis" Brit. Med. J. 2:603, 1925.

74. PRIBRAM, B.O. "Die Operative Behandeling der Mitralstenose" Arch. f. Klin. Chir. 142:458, 1926.

75. SELLORS, T.H. "Surgery of pulmonary stenosis; case in which pulmonary valve was successfully divided". Lancet. 1:988, 1948.

76. BROCK, SIR R.C. "Pulmonary valvulotomy for relief of congenital pulmonary stenosis". Brit. Med. J. 1:1121, 1948.

77. BROCK, SIR R.C. "Discussion on surgery of heart and great vessels." Proc. Roy. Soc. Med. 44:995, 1951.

78. SMITHY, H.G. and PARKER, E.F. "Experimental aortic valvulotomy - A preliminary report". Surg. Gynae. Obstet. 84:625, 1947.

79. BAILEY, C.P., GLOVER, R.P., O'NEILL, T.J.E., and RAMIREZ, H.P. "Experiences with the Experimental Surgical Relief of Aortic Stenosis". J. Thor. Surg. 20:516, 1950.

80. BAILEY, C.P. RAMIREZ, H.P. and LARZELERE , H.B. "Surgical Treatment of Aortic Stenosis". J. Amer. Med. Ass. 150:1647.

81. BROCK, SIR R.C. "Arterial Route to the Aortic and Pulmonary valves. The Mitral Route to the aortic valve." Guys Hosp. Rep. 99:236, 1950.

82. MULLER, W.H., KOTLER, A.B., DAMMAN, J.F., and SMITH, R.T. "Experiences in the Surgical Treatment of Aortic Stenosis". J. Thor. Surg. 28:516, 1954.

83. SWANN, W.K. BRADSHAW, J.T., and RODRIQUEZ-ARROYD, J. "Intracardiac Surgery with the aid of Artificial Operative Tunnels". J. Thor. Surg. 28:266, 1954.

84. MUNRO, J.C. "Ligation of the Patent Ductus Arteriosus". Ann. Surg. 46:335, 1907.

85. GRAYBIEL, A., STREIDER, J.W., and BOYER, N.H. "An attempt to obliterate the Patent Ductus Arterious in a patient with Subacute Bacterial Endocarditis". Amer. Heart J. 15:621, 1938.

86. GROSS, R.E., and HUBBARD, J.P. "Surgical ligation of a Patent Ductus Arteriousus. Report of first successful case". J. Amer. Med. Ass. 112:729,1939.

87. GROSS, R.E. "Complete division for the Patent Ductus Arteriosus". J. Thor. Surg. 16:314, 1947.

88. CRAFOORD, C., and NYLIN, G. "Congenital Co-arctation of the Aorta and its Surgical Treatment". J. Thor. Surg. 14:347,1945.

89. GROSS, R.E. "Surgical correctioh for Co-arctation of the Aorta". Surgery. 18:673, 1945.

90. BLALOCK, A., and TAUSSIG, H.B. "Surgical Treatment of Malformations of the Heart". J. Amer. Med. Ass. 128:189, 1945.

91. POTTS, W.J., SMITH, S. and GIBSON, S. "Anastomosis of Aorta to Pulmonary Artery". J. Amer. Med. Ass. 132:627, 1946.

92. MURRAY, G. "Closure of defects in cardiac septa". Ann. Surg. 28:843, 1948.

93. COHN, R. "An Experimental Method for the closure of Interauricular Septal Defect in Dogs". Amer. Heart J. 33:453, 1947.

94. SWAN, H., MARESH, G., JOHNSON, M.E., and WARNER, G. "The Experimental creation and closure of Atrial Septal Defects". J. Thor. Surg. 20:542, 1950.

95. SANTY, P., BRET, J., and MARIAN, P. cited by GROSS, R.E. "The Surgery of Infancy and Childhood". W.B. Saunders and Co., London. 1953.

96. GROSS, R.E., POMERAZ, A.A., WATKINS, E., and GOLDSMITH, E.I. "The Surgical Closure of defects of the Interauricular septum by use of an atrial well". New Eng. J. Med. 247:455, 1952.

97. LEWIS, F.J. and TAUFIC, M. "Closure of atrial septal defects with the aid of hypothermia; experimental accomplishments and the report of one successful case". Surgery. 33:52, 1953.

98. GIBBON, J.H. "Application of a Mechanical Heart and Lung Apparatus to Cardiac Surgery". Minn. Med. 37:171, 1954.

99. MELROSE, D.G., DREYER, B., BENTALL, H.H. and BAKER, J.B.E. "Elective cardiac arrest; preliminary communication". Lancet. 2:21, 1955.

100. EFFLER, D.B., GROVES, L.K., SONES, F.M., and KOLFF, W.J. "Elective cardiac arrest in open-heart surgery: report of 3 cases". Cleveland Clin. Quart. 23:105, 1956.

101. LAM, C.R. Report to the Michigan Heart Association, cited by LAM,C.R., GAHAGAN, T., SERGEANT, C., and GREEN, E. "Extracorporeal Circulation". Springfield, Illinois: Charles C. Thomas. 1958.

102. LILLEHEI, C.W., DEWALL, R.A., GOTT, V.L., and VARCO, R.L. "Direct vision correction of calcific aortic stenosis by means of pump-oxygenator and retrograde coronary sinus perfusion". Dis. Chest. 30:123, 1956.

103. LILLEHEI, C.W., COHEN, M., WARDEN, H.E., ZIEGLER, N., and VARCO, R.L. "The result of direct vision closure of ventricular septal defects in 8 patients by means of controlled. cross circulation". Surg. Gynae. Obst. 101:446, 1955.

104. WARDEN, H.E., COHEN, M., READ, R.C., and LILLEHEI, C.W. "Controlled. cross circulation for open intracardiac surgery: physiologic studies andresultsof creation andclosure of ventricular septal defects". J.Thor, Surg. 28:331, 1954.

105. CAMBELL, G.S., CRISP, N.W., and BROWN, E.B. "Maintenance of respiratory function with isolated lung lobes during cardiac inflew occlusion". Proc. Soc. Expt. Biol. Med. 88:390, 1955.

106. WARDEN, H.E., READ, R.C., DEWALL, R.A. AUST, J.B., COHEN, M., ZIEGLER,N., VARCO, R.L. and LILLEHEI, C.W. "Direct vision intracardiac surgery by means of a reservoir of arterialized venous blood". J. Thor. Surg. 30:649, 1955.

107. MILLER, B.J. GIBBON, J.H., and GIBBON, M.H. "Recent Advances in the development of a mechanical heart andlung apparatus". ANN. Surg. 134:694, 1951.

108. CROSS, E.S., BERNE, R.M., HIROSEY-JONES, R.D., and KAY, E.B. "Evaluation of a rotating disc type reservoir exygenator". Proc. Soc. Expt. Biol. Med. 93:210, 1956.

109. BROCK, SIR R.C. Henry Ford Hospital International Symposium on Cardio-vascular Surgery. W.B. Saunders Co., London. P.66. 1955.

110. MURRAY, G., WILKINSON, F.R. and MacKENZIE, R. "Reconstruction of the valves of the Heart". Canad. Med. Ass. J. 38:317, 1938.

111. MURRAY, G. "The Surgical Treatment of Mitral Stenosis". Canad. Med. Ass. J. 62:444, 1950.

112. MURRAY, G. "The Treatment of Mitral valve stenosis by resection and replacement of valve under direct vision". Arch. Surg. 61:903, 1950.

113. LOGAN, A., and TURNER, R. "The Diagnosis of Mitral Incompetence

accompanying Mitral Stenosis: Review of 11 cases treated surgically". Lancet. 2:593, 1952.

114. WILSON, W.C. "Studies in Experimental Mitral Obstruction in relation to the Surgical Treatment of Mitral Stenosis". Brit. J. Surg. 18:259, 1930.

115. TEMPLETON, J. and GIBBON, J.H. "Experimental Reconstruction of Cardiac valves by venous and pericardial grafts". Ann. Surg. 129:161, 1949.

116. BAILEY, C.P., O'NEILL, T.J.E., GLOVER, R.P., JAMISON, W.L., and REDONDO-RAMIREZ, H.P. "Surgical Repair of Mitral Insufficiency". Dis, Chest. 19:125, 1951.

117. BREWIN, E.G. "The use of Tissue Transplants in the Surgery of Cardiac Valvular Disease: An Experimental Study." Guys Hosp. Rep. 105:328, 1956.

118. MOORE, T.C., and SHUMBACKER, H.B. "Unsuitability of Transventricular autogenous slings for diminishing valvular insufficiency." Surgery. 33:173, 1953.

119. GLOVER, R.P., HENDERSON, A.R., MARGUTTI, R., and GREGORY, J. Surgical Forum, American College of Surgeons. W.B. Saunders Co., Philadelphia. p.178..1953.

120. TEDESCHI, C.G., and NAHAS, H.C. "The pericardial Graft in Mitral Insufficiency". Dis, Chest. 28:599, 1955.

121. BAILEY, C.P., LACEY, M.M. and HARRIS, J.S.C. "The Surgical Treatment

of Acquired Heart Disease". Surg. Clin. N. Amer. 31:1821, 1951.

122. BAILEY, C.P., BOLTON, H.E., and REDONDO-RAMIREZ, H.P. "Surgery of the Mitral Valve". Surg. Clin. N. Amer. 32:1807, 1952.

123. BAILEY, C.P., JAMISON, W.L., BAKST, A.E., BOLTON, H.E., NICHOLS, H.T., and GEMEINHARDT, W. "The Surgical Correction of Mitral Insufficiency by the use of Pericardial Grafts". J. Thor. Surg. 28:551, 1954.

124. HENDERSON, A.R., ASBURY-PARK, N.J., and LAW, C.L. "The Surgical Treatment of Mitral Insufficiency". Surgery. 33:858, 1953.

125. BAKST, A.A., and LOEWE, L. "Pericardial valve grafts in the surgical therapy of Mitral Insufficiency". 43rd. Annual Clinical Congress, Americal College of Surgeons, Atlantic City, New Jersey. 1957.

126. BAKST, A.L., BOLEY, S.J., JOSEPH, E., and LOEWE, L. "The Surgical Correction of Mitral Insufficiency by use of a pericardial valve graft". J. Thor. Surg. 35:493, 1958.

127. SAKAKIBARA, S. "Surgical Approach to the correction of Mitral Insufficiency". Ann. Surg. 142:196, 1955.

128. MURRAY, G. "Homalogous Aortic-valve-Segment Transplants as Surgical Treatment for Aortic and Mitral Insufficiency". Angiology. 7:466, 1956.

129. MONK, I., REEVE, T.S. KALOKERINOS, J., and WINGFIELD, J. "A preliminary

report on a study of experimentally produced Tricuspid and Mitral valve regurgitation". Brit. J. Surg. 46:75, 1958.

130. DENTON, G.R. "A plastic prosthesis (without moving parts) for the Atrio-ventricular valves". Surgical Forum, American College of Surgeons. W.B. Saunders Co., Philadelphia. p. 239. 1951.

131. DENTON, G.R. SEYMOUR, T., and WIGGERS, H. "A follow-up on the development of a Plastic Prosthesis for the Atrio-ventricular valve". Surgical Forum, American College of Surgeons. W.B. Saunders Co., Philadelphia. p. 83. 1954.

132. CARTER, M.G., GOULD, J.M., and MANN, B.F. "Surgical Treatment of Mitral Insufficiency". J. Thor. Surg. 26:574, 1953.

133. HARKEN, D.E., BLACK, H., and ELLIS, L.B. "The Surgical Coorection of Mitral Insufficiency". J. Thor. Surg. 28:604, 154.

134. HARKEN, D.E. "The Surgical Treatment of Mitral Insufficiency". Henry Ford Hospital International Symposium on Cardiovascular Surgery. W.B. Saunders Co., London. p.212. 1955.

135. BENICHOUX, R., and CHALMOT, P. "A method for the Surgical Correction of Mitral Insufficiency". J. Thor. Surg. 30;148, 1955.

136. LILLEHEI, C.W., GOTT, V.L., DEWALL, R.A., and VARCO, R.L. "The Surgical Treatment of Stenotic or Regurgitant lesions of the Mitral and Aortic valves by direct vision utilising a pump

oxygenator". J. Thor. Surg. 35:155, 1958.

137. GOTT, V.L., DEWALL, R.A., GONZALEZ, J.A., HODGES, P.C., VARCO, R.L., and LILLEHEI, C.W. "The Direct Vision Surgical correction of Pure Mitral Insufficiency by use of Annuloplasty or a valvular prosthesis". Univ. Minn. Med. Bull. 29:69, 1957.

138. BARNARD, C.N., PHILLIPS, W.L., deVILLIERS, D.R., CASSERLEY, R.D.,HEWITSON, VAN DER RIET, R., and McKENZIE, M.B. "Some experiences with intracardiac surgery using the Helix-reservoir bubble oxygenator with total cardio-pulmonary by-pass". S. Afr. Med. J. 33:789, 1959.

139. ELLIS, F.H., BRANDENBURG, R.O., CALLAHAN, J.A., and MARSHALL, H.W. "Open Heart Surgery for Acquired Mitral Insufficiency". Arch. Surg. 79:222, 1959.

140. BARNARD, C.N., McKENZIE, M.B., and SCHRIRE, V. "A Surgical Approach to Mitral Insufficiency". Brit. J. Surg. In press.

141. JOHNS, T.N.P., and BLALOCK, A., "Mitral Insufficiency: The Experimental use of a Mobile Polyvinyl-Sponge prosthesis". Ann. Surg. 140:335, 1954.

142. JORDAN, P., and WIBLE, J., "Spring valve for Mitral Insufficiency". Arch. Surg. 71:468, 1955.

143. WIBLE, J.H., JACOBSON, L.F., JOHNSTON, C.G. and HELLENS, M.K. "Spring Valve Mitral Prosthesis: Report on One Case with

one-year Follow-up". J. MICHIGAN Med. Soc. 56:731, 1957.

144. BERG, E.H., GOODMAN, E.S., STUCKEY, J.H., and NEWMAN, M.M. "Total replacement of the Mitral Valve". 43rd Annual Clinical Congress, American College of Surgeons, Atlantic City, New Jersey. 1957.

145. KERNAN, M.C., NEWMAN, M.M., LEVOWITZ, B.S., STUCKEY, J.H., and DENNIS, C. "A Prosthesis to replace the Mitral Valve". J. Thor.Surg. 33:698, 1957.

146. ELLIS, F.H., and BULBULIAN, A.H. "Prosthetic Replacement of the Mitral Valve. 1. Preliminary Experimental Observations". Proc. Staff Meet. Mayo. Clin. 33:532, 1958.

147. GLENN, W.W.L., TURK, L.N., and GENTSCH, T.O. Surgical Forum, American College of Surgeons. W.B.Saunders Co., Philadelphia. p.5. 1954.

148. GLENN, W.W.L., and TURK, L.N. "The Surgical Treatment of Mitral Insufficiency : The fate of a Vascularised Transchamber Intracardiac Graft". Ann. Surg. 141:510, 1955.

149. GLENN, W.W.L., GENTSCH, T.O., HUME, M., and GUILFOIL, P.H. "The Surgical Treatment of Mitral Insufficiency with particular reference to the Application of a vertically suspended graft". Surgery. 40: 59, 1956.

150. BAILEY, C.P., BOLTON, H.E., JAMISON, W.L., NICHOLS, H.T., and LIKOFF, W. "Methods of Surgical Treatment for Valvular Insufficiency of the Heart". Henry Ford Hospital International Symposium on Cardiovascular Surgery. W.B. Saunders Co.,

London. p.222. 1955.

151. HAYWARD, J. "A New Operation for Mitral Regurgitation". Aust. and N.Z. Jour. of Surg. 23:257, 1953.

152. BOTWIN, A.E. "Pedunculated Atrial Flaps used for Experimental Cardiac Surgery". J. Thor. Surg. 28:300, 1954.

153. SHUMWAY, N.E., and LEWIS, F.J. "Experimental Surgery of the Mitral Valve under Direct Vision using Hypothermia". Surgical Forum, American College of Surgeons. W.B. Saunders Co., Philadelphia. p.12. 1954.

154. DEWALL, R., WARDEN, H.E., LILLEHEI, C.W., and VARCO, R.L. "A Prosthesis for the Palliation of Mitral Insufficiency". Dis. Chest 30:133, 1956.

155. RUMEL, W.R., and CUTLER, P.R. "The Correction of Mitral Insufficiency with a Trans-valvular Polyvinyl Formalised Plastic (Ivalon) Sponge Prosthesis". Dis. Chest 33:401, 1958.

156. GORLIN, R., and GORLIN, S.G. "Hydraulic Formula for Calculation of the area of the stenotic Mitral Valve, other Cardiac Valves, and Central Circulatory Shunts". Amer. Heart J. 41:1. 1951.

157. BERNHEIM, B.M. "Experimental Surgery of the Mitral Valve". Bull. Johns Hopkins Hosp. 20:107, 1909.

158. SHAW, M.M., ADAMS, W.E., RASMUSSEN, R.A., HRDINA, L.S., and ARONSON, H.G. "Experimental Production of Insufficiency and Stenosis of the Heart Valves in Dogs". J. Thor. Surg. 12:322, 1942.

159. CONNOLLY, J.E. "Experimental Mitral Stenosis : A Method for its production in the Dog". Surgical Forum, American College of Surgeons. W.B. Saunders Co., Philadelphia. p.234. 1951.

160. HURWITT, E., HOFFERT, P.W. and FERREIRA, R. "Plication of the Annulus in the Correction of Mitral Valvular Insufficiency". Surgical Forum, American College of Surgeons. W.B.Saunders, Co., Philadelphia. p. 64. 1954.

161. HURWITT, E.S., HOFFERT, P.W., and FERREIRA, R. "The Experimental Production and correction of Mitral Insufficiency". Surgery. 37:15, 1955.

162. CARREL, A. "On the Experimental Surgery of the Heart and Thoracic Aorta". Ann. Surg. 52:83, 1910.

163. McALLISTER, F., and FITZPATRICK, H.F. "Construction of the Mitral Annulus in thecorrection of certain types of Mitral Insufficiency and as an aid in by-passing the left ventricle. Surgery. 40:54, 1956.

164. ELLISON, R.G., MAJOR, R.C., PICKERING, R.W., and HAMILTON, W.F. "Technique of producing Mitral Stenosis of controlled degree". J. Thor. Surg. 24:154, 1952.

165. BORRIE, J. "Experimental Circular Suture around the Atrio-ventricular ring". J. Thor. Surg. 30:687, 1955.

166. DAVILA, J.C., MATTSON, W.W., O'NEILL, T.J.E., and GLOVER, R.P. "A method for the Surgical correction of Mitral Insufficiency". Surg. Gynae. Obst. 98:407, 1954.

167. DAVILA, J.C., GLOVER, R.P., TROUT, R.G., MANSURE, F.S., WOOD, N.E., JANTON, O., and IAIA, B.D. "Circumferential Suture of the Mitral Ring". J. Thor. Surg. 30:531, 1955.

168. DAVILA, J.C., KYLE, R.H., and GLOVER, R.P. "Mitral Regurgitation due to Ruptured Chordae Tendineae; Correction by "Mitral Purse-string". Amer. Heart. J. 54:940, 1957.

169. GLOVER, R.P., "The Technique of Mitral Commissurotomy". Henry Ford Hospital International Symposium on Cardiovascular Surgery". W.B. Saunders Co., London. p. 200. 1955.

170. GLOVER, R.P.,and DAVILA, J.C. "The Treatment of Mitral Insufficiency by the Purse-string technique". J. Thor. Surg. 33:75, 1957.

171. GLOVER, R.P., and DAVILA, J.C. "The Surgical Treatment of Mitral Insufficiency by Total Circumferential Purse-string Suture of the Mitral Ring". Circulation. 15:661, 1957.

172. DAVILA, J.C. Discussion on paper by KENT, D.L., FORD, W.B., NEVILLE, J., and FISHER, D.L. Ref. 173. J. Thor. Surg. 36:429, 1958.

173. KENT, E.M., FORD, W.B., NEVILLE, J., and FISHER. D.L. "Experiences with the Davila-Glover Purse-string suture in the correction of mitral insufficiency : a critical appraisal" J. Thor. Surg. 36:421, 1958.

174. BOSHER, L.H. Discussion on paper by KENT, E.M., FORD, W.B., NEVILLE, J and FISHER, D.L. Ref. 173. J. Thor. Surg. 36:429, 1958.

175. KAY, E.B., and CROSS, F.S. "Surgical Treatment of Mitral Insufficiency". Surgery. 37:697, 1955.

176. KAY, E.B., and CROSS, F.S. "The Surgical Treatment of Mitral Insufficiency" J. Thor. Surg. 29:618, 1955.

177. FERRIN, A.L., ADAMS, W.L., and BARONOFSKY, I.D. "Evaluation of Experimental Methods of Producing Functional Mitral Stenosis". Surgical Forum, American College of Surgeons. W.B. Saunders Co., Philadelphia. p. 206. 1951.

178. NICHOLS, H.T. "Mitral Insufficiency : Treatment by Polar cross fusion of the Mitral Annulus Fibrosis". J. Thor. Surg. 33:102, 1957.

179. GILMAN, R.A., MUSSER, B.G., IMBRIGLIA, J.E., VAZQUEZ, M.J., and NICHOLS, H.T. "Experimental Study of the fusion of the mitral annulus at the site of polar cross plication in dogs". Surgery. 42:891,1957.

180. LILLEHEI, C.W. WARDEN, H.E., DEWALL, R.A., STANLEY, P., and VARCO, R.L. 1957. "Cardio-pulmonary by-pass in Surgical Treatment of Congenital or acquired Cardiac Disease". Arch. Surg. 75:928, 1957.

181. LILLEHEI, C.W. GOTT, V.L., DEWALL, R.A., VARCO,R.L. "Surgical Correction of Pure Mi tral Insufficiency by Annuloplasty under Direct Vision". Journal-Lancet. 77:446, 1957.

182. MERENDINO, K.A., and BRUCE, R.A., "One hundred and seventeen surgically treated cases of valvular rheumatic heart disease - with preliminary report of two cases of Mitral regurgitation treated under direct vision and of a pump oxygenator". J. Amer. Med. Ass. 164:749, 1957.

183. MERENDINO, K.A., THOMAS, G.I., JESSEPH, J.E., HERRON, P.W., WINTERSCHEID, L.C., and VETTO, R.R. "The open correction of rheumatic mitral regurgitation and/or stenosis. Ann. Surg. 150:5, 1959.

184. SCOTT, H.W., DANIEL,R.A., ADAMS, J.E., and SCHULL, L.G. "Surgical correction of Mitral Insufficiency under Direct Vision : report of Clinical Cases. Ann. Surg. 147:625, 1958.

185. KAY, E.B., CID NOGUEIRA, and ZIMMERMAN, H.A. "Direct Vision Correction of Mitral Insufficiency". Surgery. 44:325, 1958.

186. ROBERTSON, R. Discussion on paper by BAILEY, C.P., BOLTON, H.E., JAMISON, W.L., NICHOLS, H.T. and LIKOFF, W. Ref. 150. Henry Ford Hospital International Symposium on Cardio-vascular Surgery. W.B. Saunders Co., London. p.222. 1955.

187. CONKLIN, W.S., MAURICE, G.L., and BERQUIST, S.F. "Mitral Valve Surgery : Transventricular Valvuloplasty and use of Ivalon Sponge Pack for Mitral Insufficiency". Dis. Chest 35:291, 1959.

188. KUYKENDALL, S.J., ELLIS, F.H., and GRINDLAY, J.H. "Surgical Correction of Chronic Mitral Insufficiency in Dogs". Surgery. 3:718, 1958.

189. KUYKENDALL, S.J., ELLIS, F.H., and FRINDLAY, J.H. "The Experimental Creation of Chronic Mitral Insufficiency". Ann. Surg. 147:98, 1958.

190. BOLTON, H.E., BAILEY, C.P., JAMISON, W.L., and RAO,K. "Multivalvular Heart Disease and Simultaneous Surgical Correction". J. Int. Coll. Surg. 20:1, 1953.

191. JAMISON, W.L., and BAKST, A.E. cited by BAILEY, C.P., JAMISON, W.L., BAKST, E.A., BOLTON, H.E., NICHOLS, H.T., and GEMEINHARDT, W. Ref. 123. T. Thor. Surg. 28:551, 1954.

192. JAMISON, W.L., GEMEINHARDT, W., ALAI, J., and BAILEY, C.P. "Artificial maintenance of the Systemic Circulation without participation of the Left Ventricle". Circ. Res. 2:315, 1954.

193. EFFLER, D.B., GROVES, L.K., MARTINEZ, W.V., and KOLFF, W.J. "Open heart surgery for Mitral Insufficiency". J. Thor. Surg. 36:665, 1958.

194. LYONS, W.S., and KIRKLIN, J.W. "Surgical healing of the Atrio-ventricular leaflets - An Experimental Study". 43rd Annual Clinical Congress, American Congress of Surgeons, Atlantic City, New Jersey, 1957.

195. JAMISON, W.L. cited by BAILEY, C.P., JAMISON, W.L., BAKST, A.E., BOLTON, H.E., NICHOLS, H.T., and GEMEINHARDT, W. Ref.123. J. Thor. Surg. 28:551, 1954.

196. DODRILL, F.B. "Experiences with the Mechanical Heart". J. Amer. Med. Ass. 154:299, 1954.

197. JOHNSON, A.S. "A Simple Surgical Method for the Correction of Mitral Regurgitation using the Finger Ring Valve Elevator". J. Thor. Surg. 32:557, 1956.

198. ALBANESE, A.R. Discussion on paper by BAILEY, C.P. BOLTON, H.E., JAMISON, W.L., NICHOLS, H.T., and LIKOFF, W. Ref. 150. Henry Ford Hospital International Symposium on Cardiovascular Surgery. W.B. Saunders Co., London. p.222. 1955.

199. RAPPAPORT, A. MURRAY, J.F., DAVIES, L.S. "Atrio-ventricular anastomosis-An additional valve". Proc. Soc. Expt. Biol. and Med. 69:345, 1948.

200. BROCK. SIR R.C. "The Surgical and Pathological Anatomy of the Mitral Valve". Brit. Heart. J. 14:489, 1952.

201. JOHNSTON, T.B., and WHILLIS, J. Gray's Anatomy. 31st ed. Longmans Green and Co., London. 1954.

202. BRASH, J.C. "Cunninghams Text-book of Anatomy" 9th ed. Oxford Univ. Press. London 1951.

203. GRANT, J.C.B. "A Method of Anatomy ; descriptive and deductive" 9th ed.

Williams and Wilkins. Baltimore. 1948.

204. TANDLER, J. cited by QUAIN, Ref. 27. "Elements of Anatomy" Vol. 1V. Part 3. The Heart. 11th ed. Longmans Green and Co. London. 1929.

205. GOULD, S.E. "Pathology of the Heart". Charles C. Thomas, Publisher. Springfield, Illinois. 1953.

206. VAN DER SPUY, L. "The Functional and Clinical Anatomy of the Mitral Valve". Brit. Heart J. 20:471, 1958.

207. WALMSLEY, R. "The orientation of the Heart and the Appearance of its chambers in the Adult Cadaver". Brit. Heart J. 20:441, 1858.

208. CHIECHI, M.A., LEES, W.M., and THOMPSON, R. "Functional Anatomy of the Normal Mitral Valve". J. Thor. Surg. 32:378, 1956.

209. RUSTED, I.E., SCHEIFLEY, C.H., and EDWARDS, J.E. "Studies of the Mitral Valve. 1. Anatomic features of the Normal Mitral Valve and Associated Structures". Circulation 6:825, 1952.

210. HARKEN, D.E., ELLIS, L.B., DEXTER, L., FARRAND, R.E., and DIKSON, J.F. "The responsibility of the Physician in the Selection of Patients with Mitral Stenosis for Surgical treatment" Circulation. 5:349, 1952.

211. KUGEL, M.A., and GROSS, L. "Gross and microscopical anatomy of the blood vessels in the valves of the human heart". Amer.

Heart. J. 1:304, 1925.

212. WEARN, J.T., BROMER, A.W., and ZSCHIESCHE, L.J. "The Incidence of blood vessels in human heart valves". Amer. Heart J. 11:22, 1936.

213. KOLETSKY, S. "Gross vascularity of the Mitral Valve as a Stigma of Rheumatic Heart Disease". Amer. J. Path. 22:351, 1946

214. SOKOLOFF, L., ELSTER, S.K., and RIGHTHAND, N. "Sclerosis of the Chordae Tendineae of the Mitral Valve". Circulation 1:782, 1950.

215. MALL, F.P. "On the Muscular Architecture of the Ventricles of the Human Heart". Amer. J. Anat. 11:211, 1911.

216. RUSTED, I.E., SCHEIFLEY, C.H., and EDWARDS, J.E. "Guides to the Commissures in Operations upon the Mitral Valve". Proc. Mayo Clin. 26:297, 1951.

217. SMITH, H.L., ESSEX, H.E., and BALDES, E.J. "A Study of the movements of the heart valves andof heart sounds". Ann. Int. Med. 33:1357, 1950.

218. KANTROWITZ, A., HURWITT, E.S., and HERKOVITZ, A. "A cinematographic study of the function of the Mitral Valve in situ". Surgical Forum, American College of Surgeons. W.B. Saunders Co., Philadelphia. p. 204. 1951.

219. GUYTON, A.C. "Textbook of Medical Physiology". W.B. Saunders Co., Philadelphia. 1956.

220. HENDERSON, Y., and JOHNSON, F.E. "Two modes of closure of the heart valves". Heart. 4:69, 1912.

221. WIGGERS, C.J. "Circulation in Health and Disease". 2nd. ed. Lea. Philadelphia. 1923.

222. KREHL, L. cited by LITTLE, R.C. Ref. 225. Amer. J. Phys. 166:289, 1951.

223. STRAUB, H. cited by LITTLE, R.C. Ref. 225. Amer. J. Phys. 166:289, 1951.

224. RUSHMER, R.F. FINLAYSON, B.L., and NASH, A.A. "Movements of the Mitral Valve". Circulation Res. 4:337, 1956.

225. LITTLE, R.C. "Effect of Actual Systole on Ventricular Pressure and Closure of the Atrio-ventricular valves". Amer. J. Phys. 166:289, 1951.

226. BAILEY, C.P. "Surgery of the Heart". Lea and Febiger, Philadelphia. 1955.

227. BEST, C.H., and TAYLOR, N.B. "The Physiological Basis of Medical Practice". 6th ed. The Williams and Wilkins Co., Baltimore. 1955.

228. DAVILA, J.C., TROUT, R.G., SUNNER, J.E., and GLOVER, R.P.. "A simple mechanical Pulse-duplicatoe for cinematography of Cardiac Valves in action". Ann. Surg. 143:544, 1956.

229. LUTEMBACHER, R. "Le Rétréissement Mitral". Paris. 1950.

230. McKENZIE, M.B., and BARNARD, C.N. "Induced Ventricular Fibrillation, an experimental study with special reference to the use of this technique for the prevention of systemic air-embolism".

S. Afr. J. Lab. and Clin. Med. In press.

231. STARKEY, G.W.B. "Surgical Experiences in the Treatment of Congenital Mitral Stenosis and Mitral Insufficiency". J. Thor. Surg. 38:336, 1959.

232. EDWARDS, J.E. and BURCHELL, H.B. "Pathologic Anatomy of Mitral Insufficiency." Proc. Staff Meet. Mayo Clin. 33:497, 1958.

233. BARBER, H. "The effects of Trauma, Direct and Indirect, on the Heart". Quart, J. Med. (new series). 13:137, 1944.

234. HORTON-SMITH, P. cited by BARBER, H. "Trauma of the Heart". Brit. Med. J. 1:433, , 1938.

235. FROTHINGHAM, C., and HASS, G.M. "Rupture of the Normal Chordae Tendineae of the Mitral Valve". Amer. Heart. J. 9:492, 1934.

236. KISSANE, R.W. and KOONS, R.A., "Rupture of the Chordae Tendineae of Normal Mitral Valve, Case report". Ohio State Med. J. 34:303, 1938.

237. ADAM, A. cited by BAILEY, C.P. "Surgery of the Heart" Lea and Fibiger, Philadelphia. 1955.

238. GLENDY, R.E., and WHITE, P.D. "Non-penetrating wound of the heart; Rupture of Papillary muscle and contusion of heart resulting from external violence. Amer. Heart. J. 11:366, 1936.

239. BERBLINGER, W. "Ueber traumatische inkomplete Herzrupture und Mitralsegalzeireissung". Deutsch. med. Wchnschr. 36:1316,1910.

240. ANDERSON, R.G. "Non-penetrating injuries of the heart". Brit. Med. J. 2:307, 1940.

241. CAMERON, R.A. Personal communication to BARBER,H. "The effects of trauma, direct or indirect, on the heart. Quart. Jour. Med. (New series) 13:137, 1944.

242. SHAW, A.F.B. "Topography and pathogenesis of lesions in rheumatic fever". Arch. Dis. Child. 4:155, 1929.

243. GROSS, L., and FRIEDBERG, C.K. "Lesions of the Cardiac valves in rheumatic fever". Amer. J. Path..12 :469, 855, 1936.

244. BOYD, W. "A textbook of Pathology". Henry Kimpton, London. 1947.

245. TWEEDY, P.S. "The Pathogenesis of valvular thickening in rheumatic Heart Disease". Brit. Heart J. 18: 173, 1956.

246. BRIGDEN, W., and LEATHAM, A. "Mitral Incompetence" Brit. Heart J. 15:55, 1953.

247. WHITE, P.D. "Heart Disease" The Macmillan Company, New York. 1951.

248. HALL, E.M. In ANDERSON, W.A.D. "Pathology" The C.V. Mosby, Co., St Louis. 1953.

249. GOULD, S.E. "Pathology of the Heart" Charles C. Thomas, Springfield, Illinois, U.S.A. 1953.

250. WOOD, P. "Diseases of theHeart and Circulation". Eyre and Spottiswoode, London. 1956.

251. PARAVISINI-PARRA, J., AVELLANA-VECIANA, S., OBRADORS-VENTURA, J., and

GILBERT-QUERALTO, J. cited by BAILEY, C.P., JAMISON, W.L., BAKST, E.A., BOLTON, H.E., NICHOLLS, H.T., and GEMEINHARDT, W. Ref. 123. J. Thor. Surg. 28:551, 1954.

252. CZIRER, L. "Ueber die Ueränderungen an den Herzhloppen bei akuten Infektions-krankhieten". Virchows Arch. f. Path. Anat. 213:272, 1913.

253. DE VECCHI, B. "The Endocarditic Process in Childhood". Arch. Path. 12:49, 1931.

254.and 255. SAPHIR, O. "Myocarditis : A general review with an analysis of 240 cases". Arch. Path. 32:1000, 1941.
33:88. 1942.

256. MOORE, R.A. "Cellular mechanism of recovery after treatment with penicillen : subacute bacterial endocardidtis". J. Thor. and Clin. Med. 31:1279, 1946.

257. THAYER. W.S. "Bacterial or infective endocarditis". Edinbururgh Med. J. 38:237, 1931.

258. DEGOWIN, E.L., CARTER, J.R., and BORTS, I.H. "A case of infection with Brucella suis, causing endocarditis and nephritis; death from rupture of mycotic aneurysm". Amer. Heart. J. 30;77, 1945.

259. GROSS, L. and FRIED, B.M. "Role played by Rheumatic fever in emplantation of bacterial endocarditis". Amer. J. Path. 13:769, 1937.

260. CLAWSON, B.J. "Rheumatic Heart Disease: Analysis of 796 cases". Amer. Heart J. 20;454, 1940.

261. STAEMMLER cited by BLACKMAN, S.S. Bull. Johns Hopkins Hosp. 57:111, 1935.

262. BLACKMAN, S.S. "Syphilis of the Mitral Valve and Membranous septum of the Heart". Bull. Johns Hopkins Hosp. 57:111, 1935.

263. SPAULDING, E.D., and VON GLAUN, W.C. "Syphilitic Rupture of a Papillary Muscle of the Heart". Bull. Johns. Hopkins Hosp. 32:30, 1921.

264. EDWARDS, J.E. "Pathologic Aspects of Cardiac Valvular Insufficiences". Arch. Surg. 77:634, 1958.

265. WIGGERS, C.J. "Dynamics of Ventricular Contraction under Abnormal Conditions". Circulation. 5:321, 1952.

266. STARLING, E.H. "The law of the Heart Beat". Longmans, Green and Co., London. 1918.

267. BECKER, D.L., BURCHELL, H.B., and EDWARDS, J.E., "Pathology of the Pulmonary Vascular Tree : 11. The Occurrence in Mitral Insufficiency of occlusion Pulmonary Vascular Lesions." Circulation. 3:230, 1951.

268. STEELL, G. "Textbook on Diseases of the Heart." Manchester University Press. 1906.

269. MACKENZIE, SIR JAMES. "Principles of Diagnosis and Treatment of Heart Afflictions". 2nd. impression. Oxford Medical Publications. London, 1916.

270. LEWIS, Sir T. "Diseases of the heart". MacMillan, London. 1933.

271. PARKINSON, SIR JOHN. "Rheumatic fever and heart disease". Lancet 2:657, 1945.

272. CABOT, R.C. "Facts on the Heart". W.B. Saunders Co., Bhiladelphia 1926.

273. WOOD, P. "An appreciation of Mitral Stenosis" Brit. Med. J. 1:1051, 113, 1954.

274. BARNARD, C.N. "The aortic valve - problems in the fabrication and testing of a prosthetic valve". M.S. Thesis. University of Minnesita. 1958.

275. McMILLIAN, I.K.R., DALEY, R., and MATTHEWS, M.B. "The movement of Aortic and Pulmonary valves studied post mortem by colour cinematography". Brit. Heart J. 14:42, 1952.

276. McMILLAN, I.K.R. "A post mortem cinematographic study of valve action Brit. Heart J. 17:56, 1955.

277. DAVILA, J.C. TROUT, R.G., SUNNER, J.E., GLOVER, R.P. "A simple mechanical pulse-duplicator for cinematography of cardiac valves in action". Ann. Surg. 143:544, 1956.

278. BARNARD, C.N., McKENZIE, M.B., de VILLIERS, D.R. "The electrical pulse-duplicator - its use in testing valve prostheses with special referenceto the aortic and mitral valves". S. Afr. Med. J. 33:859, 1959.

279. McKENZIE, M.B., and BARNARD, C.N. "Experimental studies in extra-corporeal circulation using the Helix-reservoir bubble

oxygenator". S. Afr. Med. J. 32:1145, 1958.

280. McKENZIE, M.B. and BARNARD, C.N. "A note on priming the DEWALL oxygenator". S. Afr. Med. J. 34:108, 1960.

281. NICHOLS, H.T., MORSE, D.P., and HIROSE, T. "Coronary and other air-embolisation occurring during open cardiac surgery". Surgery. 43 :236, 1958.

282. MILLER, B.J. GIBBON, J.H, GRECO, V.F. COHEN, C.H., and ALLBRITTEN, F.F. "Use of a vent for the left ventricle as a means of avoiding air-embolism to the systemic circulation during open cardiotomy with the maintenance of the cardio-respiratory function of animals by pump-oxygenator". J. Thor. Surg. 28:235, 1954.

283. KAY, E.B., NOGUEIRA, C., HEAD, L.R., COENEN, J.P., and ZIMMERMAN, H.A. "Surgical treatment of Mitral Insufficiency". J. Thor. Surg. 36:677, 1958.

284. MILLER, B.J., GIBBON, J.H., GRECO,V.F., COHN, C.H., and ALLBRITTEN, F.F. "The use of a vent for the left ventricle as a means of avoiding air-embolism to the systemic circulation during open cardiotomy with the maintenance of the cardio-respiratory function of animals by a pump-oxygenator". Surgical Forum, American College of Surgeons, Philadelphia. W.B. Saunders and Co., p.29. 1953.

285. BAHNSON, H.T., SPENCER, F.C., and ANDRUS, E.G. "Diagnosis and Treatment

of Intracavitary Myxomas of the Heart". Ann. Surg. 145:915, 1-57.

286. LEVOWITZ, B.S., NEWMAN, M.M., STUCKEY, J.H., KERNAN, M.C., ITICOVICI, H.N. and DENNIS, C., "A mechanical pump-oxygenator for direct vision repair of atrial septal defects". J. Thor. Surg. 32:647, 1956.

287. MOORE, R.M., and BRASELTON, C.J. "Injection ofair and Carbon dioxide into a pulmonary vein". Ann. Surg. 122:212, 1949.

288. STAUFFER, H.M., DURANT, T.M., and OPPENHEIMER, M.J. "Gas embolism, Poentgenologic Considerations.Including the Experimental Use of Carbon Dioxide as an Intracardiac Contrast Material". Radiology. 66:686, 1956.

289. GUIDRY, L.D., CALLAHAN, J.A., MARSHALL, H.W., and ELLIS, F.H. "The surgical treatment of Mitral Insufficiency by Mitral Annuloplasty". Proc. Staff Meet. Mayo. Clinic 33:523, 1958.

290. EFFLER, D.G., GROVES, L.K., SONES, F.M., KNIGHT, H.F., and KOLFF, W.J., "Elective Cardiac Arrest - an adjunct to open heart surgery". J. Thor. Surg. 34:500, 1957.

291. SENNING, A. "Ventricular Fibrillation during Extracorporeal Circulation" Acta Chir. Scand. Supp. 171., 1952.

292. KAPLAN, S., CLARKE, L.C., MATTHEWS, E.C., EDWARDS, F.K., SCHWAB, L., and HELMSWORTH, J.A., "A comparison of the result of

total body perfusion in dogs during potassium citrate cardiac arrest, sinus rhythm and induced ventricular fibbrillation". Surgery. 43:14, 1958.

293. CRAFOORD, C., Personal communication to GOLDBERG, H.P., and STEINBERG, I., "Primary tumours of the heart". Circulation. 11:963, 1955.

ACKNOWLEDGEMENTS.

Experimental work of this nature would not have been possible but for the co-operation of many of my friends and colleagues. I am greatly indebted to the following for the assistance they have so willingly given me:

Dr. Chris Barnard, Director of Surgical Research at the University of Cape Town, at whose suggestion this investigation was undertaken, for his constant encouragement and invaluable advise and criticism.

Professor J.H. Louw, Professor of Surgery, University of Cape Town, who made it possible for me to spend 10 months engaged in full-time research, at the experimental laboratories of the Department of Surgery.

Mr C. Goosen and the technical staff of the Animal Laboratory, for their assistance with the animal experiments. Mr. Goosen has in addition taught me the rudiments of, and assisted with much of, the photography.

Mr J. Linney for his interest and encouragement and especially for cine photography of valves in the pulse-duplicator.

Messrs. M. Lloyd and A. de Wet of the S.A.R. and H. Workshops Salt River, Cape Town, for their work on the moulds for the manufacture of Silastic valves.

Drs S. Cywes, D.R. de Villiers and J. Terblanche for assistance at animal operations.

The staff of the Department of Pathology, University of Cape

Town for allowing me access to post-mortem material.

Miss S. Cleghorn, for assisting with the typing of the manuscript.

Finally, I am indebted to Denise, my wife, who has constantly encouraged me and who has at various times assembled and operated the oxygenator, acted as surgical assistent during animal operations, helped with the manufacture of Latex valves, assisted in the dark-room, and drawn the diagrams which appear in the text. In addition she has also typed the major portion of the amnuscript.

The expenses of this investigation were in part defrayed by a grant from the J.S. Marais Memorial Research Fund.

Publications by Malcolm Bett McKenzie.

1. McKENZIE, M.B. "Peptic Ulceration in the African of Durban", S. Afr. Med. J. 31:1041, 1957.

2. McKENZIE, M.B. and BARNARD, C.N. "Experimental Studies in Extracorporeal Circulation Using the Helix - reservoir Bubble Oxygenater", S. Afr. Med. J. 32:1145, 1958.

3. McKENZIE, M.B. "Developement of Cardiac Surgery", Med. Proceedings, 5:171, 1959.

4. BARNARD, C.N., PHILLIPS, W.L., de VILLIERS, D.R., CASSERLEY, R.D., HEWITSON, R.P., van der RIET, R.L., and McKENZIE, M.B. "Some Experiences with Intracardiac Surgery Using the Helix- Reservoir Bubble Oxygenator with Total Cardio-Pulmonary Bypass", S. Afr. Med. J. 33:789, 1959.

5. BARNARD, C.N., McKENZIE,M.B., de VILLIERS, D.R. "The Electrical Pulse-Duplicator - its use in Testing Valve Prostheses with Special Reference to the Aortic and Mitral Valves", S. Afr. Med. J. 33:859, 1959.

6. McKENZIE, M.B. and BARNARD, C.N. "A Note on Priming the DeWall Oxygenator", S. Afr. Med. J. 34:108, 1960.

7. BARNARD,C.N., SWANEPOEL, A., McKENZIE, M.B., PHILLIPS, W.L. "Left Atrial Myxoma: Report of a Case Successfully Treated Using Extracorporeal Oxygenation", Brit. J. Surg. In press.

8. McKENZIE, M.B., BARNARD, C.N. "Induced Ventricular Fibrillation - an Experimental Study with Special Reference to the Use of this Technique for the Prevention of Systemic Air Embolism", S. Afr. J. of Lab. and Clin. Med. In press.

9. BARNARD, C.N., McKENZIE, M.B. and de VILLIERS, R.D. "Stainless-steel Sponge Debubbler for use in the Helix-reservoir Pump-Oxygenator", Thorax. In press.

10. BARNARD, C.N., McKENZIE, M.B., and SCHRIRE, V. "A Surgical Approach to Mitral Insufficiency", Brit. J. Surg. Accepted for publication.

11. BARNARD, C.N., McKENZIE, M.B. "A Surgical Approach to Mitral Insufficiency", To be published in French at the request of Dr. Heim deBalsac, Director, Institute Chirurgical Marie-Lannelongue, Paris. (French translation by Dr. Heim deBalsac.)

12. McKENZIE, M.B. "The DeWall Oxygenator", Paper read at a Symposium on Open Heart Surgery, Johannesburg, Feb. 1959.

13. McKENZIE M.B. BARNARD, C.N. "The Mitral Valve, with Special Reference to Problems in the Surgical Correction of Mitral Regurgitation", Paper read at 42nd S. Afr. Medical Congress, October 1959.

Summary of a thesis entitled, "The Mitral Valve - An Experimental Study With Special Reference To Problems in the Design and Testing of a Mobile Prosthesis for the Surgical Correction of Mitral Insufficiency", by Malcolm Bett McKenzie.

1. Despite the remarkable advances in cardiac surgery during recent years, suitable techniques for the correction of all pathological types of mitral insufficiency have not yet been established. In many cases, complete correction can be effected by relatively simple surgical techniques, but the complete solution to this problem awaits the developement of a suitable mobile prosthesis.

2. A detailed post-mortem study of the anatomy of the normal valve and the pathological anatomy of the incompetent valve was carried out, and valve action was studied at open operation and by means of an artificial pulse-duplicator, designed for the purpose. As a result of these studies it was decided to design and test a simple flap type valve, which would be fixed to the postero-lateral sector of the mitral annulus fibrosus. Such a valve should not interfere with the complex relationships of the antero-medial portion of the mitral annulus, or the normal sphincter-like action of the valve ring, and should be activated by the haemo-dynamic forces normally active within the chambers of the heart.

3. The use of intra-cardiac tissue grafts having been shown by numerous previous workers to be unsatisfactory, it was decided to use an artificial material for the fabrication of the prosthesis. Silastic -

a pliable, durable, inert silicone-rubber compound - was found to be the most satisfactory artificial substance available. The fabrication of Silastic valves soon proved to be costly and time-consuming and a technique for the fabrication of Latex-rubber valves for preliminary experiments was therefore devised.

4. A suitable technique for the insertion of valves in experimental animals was devised. All operations were performed under direct vision using the Helix-reservoir bubble oxygenator. A direct left-sided approach to the mitral valve was found to be superior to a right thoracotomy approach in the normal dog. The use of elective ventricular fibrillation was found to be a safe and reliable technique for the prevention od systemic air-embolism, a recognised complication of open left atriotomy.

5. Silastic and Latex-rubber flap type valves were designed and manufactured, and their action studied in hearts set up in the artificial pulse-duplicator and in experimental animals. Defects in valve design were detected and modifications effected as indicated until a mechanically efficient Silastic valve was developed. Prolonged action in the pulse-duplicator proved that such a valve was durable, and experimental operations on dogs confirmed that the valve was easy to insert in the desired position within the heart. All these animals however developed intra-cardiac thrombosis within

6 - 16 days of the operation.

6. It is concluded that a Silastic flap valve (Valve V) sutured to the postero-lateral portion of the mitral annulus fibrosus, although mechanically efficient, durable, and easy to insert in the desired position within the heart, is at present unsuitable for clinical use as it causes intra-cardiac clot formation. If this complication can be prevented such a valve may be employed clinically for the correction of those pathological types of mitral insufficiency, which are not able to be corrected by surgical techniques at present available.