A STUDY OF THROMBO-EMBOLIC COMPLICATIONS FOLLOWING TOTAL MITRAL VALVE REPLACEMENT WITH THE UNIVERSITY OF CAPE TOWN LENTICULAR MITRAL PROSTHESIS.

T H E S I S

F O R T H E D E G R E E O F M A S T E R
O F S U R G E R Y ,

Presented by

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INTRODUCTION.

I N T R O D U C T I O N.

Rheumatic involvement of the mitral valve is the commonest cause of acquired valvular disease of the human heart. The life expectancy of these patients is considerably shortened: it is estimated that 39% will die within 10 years, in spite of expert medical treatment (Effler et al, 1965). As the disease progresses, the prognosis rapidly assumes graver proportions. Reporting a study of 351 patients in functional Class II and III (New York Heart Association classification), Olesen (1955) showed that 19% were dead within 2 years, and 38% within 5 years. Among the patients falling into Class IV, 50% died within 2 years and 90% within 5 years. Rowe and his associates (1960) reviewed the histories of 250 patients suffering from mitral stenosis over a period of 20 years: 52% of those in functional class III were dead within 2 years, and 63% within 5 years. Only 15% were alive after 10 years.

In addition to a poor life expectancy, the morbidity among patients suffering from acquired mitral valve disease is considerable. They soon become cardiac cripples, forced to sleep in a sitting position, their physical activities restricted to the minimum, and they require periodic hospitalisation.

The temporary and poor response to medical treatment, and the mechanical nature of this affliction, has brought these patients into the realm of the surgeon.

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Studies of normal mitral valve function, conducted in our laboratory with the help of a pulse duplicator, have shown that for all practical purposes this is nothing more than a flap type valve (Barnard et al, 1961). Closure is effected mainly by the freely mobile anteromedial leaflet, which is much longer than the posterolateral leaflet. Its chordae are attached only to the peripheral zone and a triangular area at the base (which is much thinner) is left free to billow towards the left atrial cavity during systole. The shorter posterolateral cusp - its chordae inserted more widely on its ventricular surface - moves only a short distance into the valve orifice during systole. It acts mainly as a ridge or shelf against which the anteromedial cusp abuts to effect closure (Barnard et al, 1961; Van der Spuy, 1958; Brock, 1952). The movement of the leaflets is activated by the difference in hydrostatic pressure between the atrium and the ventricle. The leaflets are passively restrained by their anchoring chordae and papillary muscles. These anchors are afforded some protection from the full force of ventricular systole by the support which the two leaflets provide for one another.

Any derangement in the normal anatomy will result in mitral valve dysfunction. Immobility of the flap, due to commissural fusion, produces stenosis. Several different pathological factors may result in incompetence of the mitral valve, but the essential cause is a deficiency of leaflet tissue - either absolute or relative or a combination of both.

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Absolute deficiency of leaflet tissue may result from a cleft, a perforation or a tear of the cusp, but more commonly results from rheumatic scarring. The posterolateral cusp is more susceptible to the ravages of the rheumatic process, but this may be more apparent than real, because of the greater length of the anteromedial leaflet (Barnard and Schrire, 1961).

Relative deficiency of mitral leaflet tissue may be due to dilatation of the annulus. The two cusps are thus moved further apart and, although there may be no actual loss of tissue, the distance the cusps must cover to meet is too great. Inflammatory changes in the junctional tissue - causing thickening, shortening and fusion of the chordae with limitation of cusp mobility - also results in relative deficiency of cusp tissue.

At present, most cardiac surgeons are agreed that mitral stenosis may be relieved readily by closed mitral valvotomy. When mitral incompetence is present, however, whether combined with stenosis or not, cardiopulmonary bypass is required for the accurate assessment of the lesion, and then the most suitable surgical procedure can be carried out. The aim of the surgeon should be to restore any relative or absolute deficiency of leaflet tissue. This can be achieved by one or more of the following techniques:-

(1) Repair of cleft, hole or tear,

(2) Mobilisation of the anteromedial cusp,

(3) Provision of a posterior shelf, or support to the anteromedial cusp,

(4) Insertion of a complete prosthesis.

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In most cases of acquired mitral valve disease the anteromedial cusp retains sufficient mobility to allow adequate correction of the defect by some plastic procedure, with or without the insertion of an immobile posterior "baffle" type prosthesis (Barnard et al, 1961; Barnard and Schrire, 1961). In others, extensive disease of the anteromedial cusp immobilises this important structure permanently, and in such cases only total replacement of the valve with some form of mobile prosthesis restores adequate function. This method of therapy has become possible in recent years as a result of the development of different prostheses for complete replacement of the mitral valve (Starr et al, 1961; Barnard et al, 1962).

The initial reports of total mitral valve replacement in human-beings were enthusiastic (Starr et al, 1962; Barnard et al, 1963) and it was hoped that by means of this procedure the surgeon would be able to cure instead of palliate the lesion. However, long-term results (Herr, 1965; Barnard et al, 1965) showed that this goal has not been achieved.

A major obstacle to the more general use of total mitral valve replacement is the alarming incidence of thrombo-embolic phenomena which occur post-operatively. Peripheral emboli as a result of small thrombi are so frequent that this complication must be recognised as part of the natural history of mitral valve replacement.

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This study was designed to investigate the major problem mentioned above: thrombus formation after insertion of the University of Cape Town (U.C.T.) mitral prosthesis. Because the dog has such a marked tendency to thrombus formation, it was felt that this animal would be an exceptionally good model in which to study this complication.

A REVIEW OF THE LITERATURE.

A REVIEW OF THE LITERATURE.

Denton (1952) first reported the experimental use of a prosthesis in the mitral area. Tubular polyethelene plastic prostheses were inserted into the left atrio-ventricular ring without cardiopulmonary bypass, in dogs. The prosthesis was inserted blindly through the atrial appendage, being secured with three sutures passed through the ventricle. The mitral valve was not excised. No reaction or thrombus was observed except in and immediately around the suture grooves, in dogs surviving up to 6 months.

After the development of temporary extracorporeal circulation with all its advantages, a number of attempts were made to replace the mitral valve both experimentally and clinically. A wide variety of valves and several different methods of insertion have been used.

TOTAL MITRAL VALVE REPLACEMENT WITH PROSTHETIC VALVES.

Two basic types of prosthetic valve (with variations) have been evolved:- (a) flap valves, and (b) ball valves.

A. EXPERIMENTAL.

(a) FLAP VALVES:

A number of investigators attempted to replace the mitral valve with various flap type valves. To prevent eversion into

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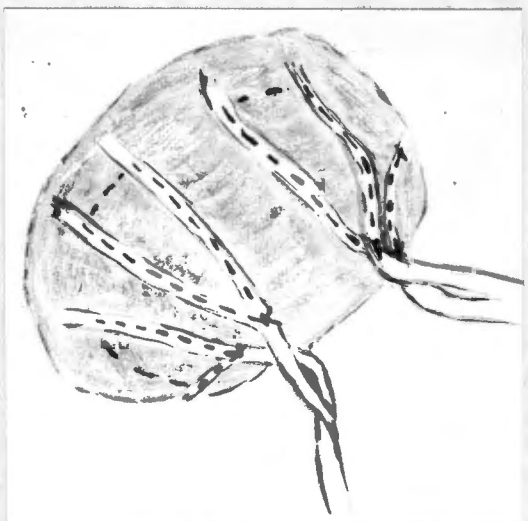
the atrium during ventricular systole, the flap(s) must either be anchored below the mitral annulus by artificial chordae, or above the annulus to some form of rigid ring. Flap valves may thus be sub-divided into (1) those incorporating artificial chordae tendineae, and (2) those not incorporating artificial chordae tendineae.

(1) <u>Flap valves incorporating artificial chordae tendineae</u>:-

Fig. 1



Drawing of flap valve incorporating artificial chordae tendineae; only one leaflet is shown. (Braunwald et al, 1960).

It was thought that a prosthesis closely resembling the anatomy of the normal mitral valve would probably provide the best functional substitute. Such a design takes advantage of ventricular contraction as well as the pressure differences between atrium and ventricle.

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Braunwald and his associates (1960) carefully prepared wax or plaster casts of the mitral valve ring and leaflets of normal fresh dog hearts. The cast was trimmed and smoothed, and two piece moulds made of Dacron. In constructing the prosthesis, a thin piece of knitted Dacron was stretched over the male half of the mould and secured around its base. "Chordae tendineae" fashioned from Teflon tape were sutured to the leaflets. These valves were used for complete mitral replacement in 27 dogs. Only 4 lived for from 8 to 40 hours after operation, due to the great technical difficulties of insertion. Necropsy revealed the valve surface to be covered with a thin layer of fibrin; there was no evidence that death resulted from mitral incompetence or stenosis.

Working along similar lines, Siedel and his colleagues (1962) evolved a smooth polyurethane valve with polyurethane-covered Dacron "chordae". One dog survived for 6 months before the prosthesis ruptured. Three animals died between 2 and 3 weeks after surgery. At necropsy, thrombus was present on the suture line.

(2) <u>Flap valves not incorporating artificial chordae tendineae</u>:-

This category may be sub-divided into the following groups:

(i) Monocusp,

(ii) Multicusp - bicuspid,
tricuspid,
quadricuspid.

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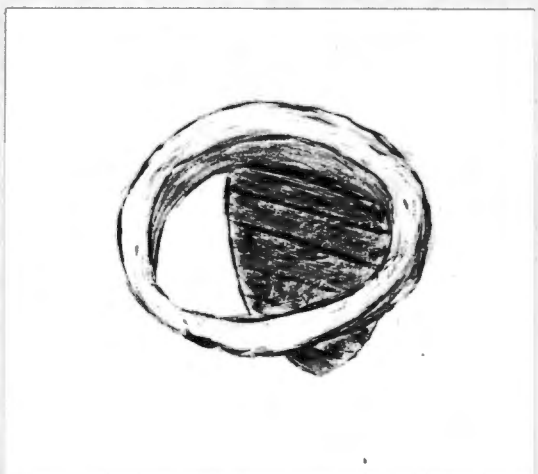
(i) Monocusp Flap Valves. (Fig. 2).

Developing a hinged, monocusp prosthetic mitral valve made of different materials, Berg et al (1957) secured this in the mitral annulus with a purse-string suture. Not one of the 46 dogs used in their study survived longer than 30 days. Except for surgical error, the major cause of death was flap fracture, fixation failure and thrombus formation which occluded the orifice.

Fig. 2.



Drawing of monocusp flap valve.
(Frater et al, 1960).

A number of workers experimented with this type of prosthesis subsequently. Modification of insertion techniques, with and without anticoagulant therapy post-operatively, changes in design and the use of a variety of materials, were the subjects of further reports. However, very little improvement in the results was noted; thrombosis and embolisation soon occurred, or the valve soon proved deficient in durability (Frater et al, 1960; Stuckey et al, 1960; Doumanion et al, 1960; Kay et al, 1960).

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Frater et al (1960) devised a flexible monocusp valve with multiple hinges. This unsupported Mylar cusp tended to fracture and was thus covered with knitted Teflon cloth (Ellis et al, 1961).

Haemodynamically, monocusp flap valves function satisfactorily and (especially using anticoagulants) an occasional long-term survivor was reported (Doumanion et al, 1961). These authors made the important observation that thrombus formation falls into two types: massive thrombosis occurring within 5 to 8 days of surgery, and thrombus occurring 1 to 2 months post-operatively over the cusp and along the inferior surface of the ring. In the latter, the orifice was not occluded and death was due to insufficiency as a result of the thrombus obstruction, preventing complete closure of the cusp against the ring. They concluded that the experimental results could be improved in three ways: by improving the method of insertion, by the use of anticoagulants and by modification of the size of the prosthesis (thrombus formation being less frequent when the ring circumference was larger than 6.2 mm.).

Malowney et al (1965) designed a Silastic monocusp prosthesis in such a way to ensure that the flap is normally open 30 to 40°, eliminating the necessity for increased atrial pressure or gravity to open it. Of the 22 dogs experimented with, only 13 survived more than 24 hours. Three were given anticoagulants and survived for between 3 and 12 weeks. All late deaths were due to massive thrombosis at the valve orifice. Thrombus formation was not found

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to be influenced by heparinisation of the animal, and haemorrhagic complications made long-term prophylaxis difficult to manage. The administration of dicoumaral appeared to prolong survival and to diminish the deposition of fibrin on the prosthetic valve.

(ii) Multicusp Flap Valves.

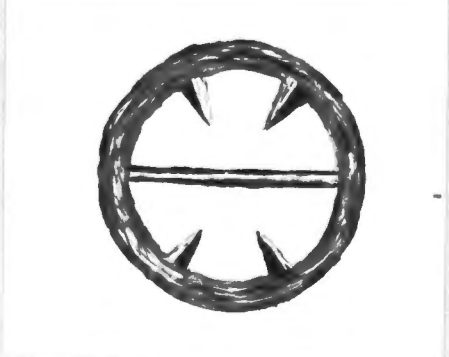
These were designed with two, three or more cusps.

(1) Bicuspid Valves: (Fig. 3).

In 1960, Starr reported the development of this type of prosthesis and the results he had obtained. Initially, the prosthesis was made from a rigid Teflon ring frame with two silicone rubber leaflets and a bar across the lumen. This was found too large for canine mitral valve replacement. A smaller version was designed and inserted into 6 dogs. One animal died due to incorrect placement and two as a result of haemorrhage. The remaining 3 dogs died within a short time due to thrombosis with acute pulmonary oedema.

The same workers then redesigned this valve, hinging the leaflets on the periphery, and inserted it in 3 dogs. Not one survived longer than 4 days after operation.

Fig. 3.



Drawing of bicuspid flap valve hinged by a bar across the lumen. (Gott et al, 1964).

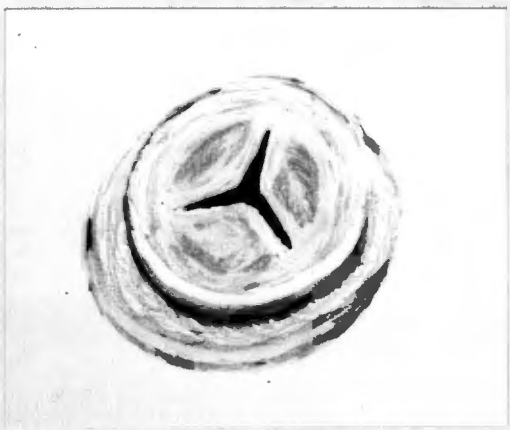
The final modification of the bicuspid valve design was to make the ring of stainless steel instead of Teflon. Of the 3 dogs in this series, only 1 survived operation and this animal died on the 4th post-operative day, as a result of thrombosis.

Similar problems were encountered by Frater et al (1961) who used a similar design.

(2) Tricuspid Valves: (Fig. 4).

In an attempt to duplicate the anatomy of the normal mitral valve, Akutsu and his associates (1959) used a plastic valve with three pliable leaflets, patterned on the semilunar heart valves. They used different materials, with and without siliconisation. The longest survival obtained was 9 days and, in most animals which survived more than 24 hours, a thick fibrin deposition was found on both sides of the valve at necropsy.

Fig. 4.



Drawing of tricuspid flap valve with three pliable leaflets, patterned on the semilunar heart valves. (Akutsu et al, 1959).

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The advantages of the leaflet (or cusp) type valve are that there is much less inertia in opening and closure, and closure of the valve is prompt. Furthermore, they occupy little space since the moving parts of the valve do not have to be propelled into the ventricle and back. The great disadvantage is that the free edges of the cusps have to support one another during high pressure closure and, as the free edge is the thinnest portion of the leaflet, rupture is prone to occur. To avoid this, a tricuspid valve was designed suspending the leaflets on pillars in the centre of the valve, closure being achieved by the leaflets hugging the annulus. This significantly increased the longevity of the prosthesis but did not prevent thrombus formation (Ernst et al, 1963).

(3) Quadricuspid Valves: (Fig. 5)

Drawing of quadricuspid valve (Levowitz et al, 1960).

Fig. 5.

Levowitz et al (1960) reported their experience with different types of multicusp flap valves. Using bicuspid, tricuspid, quadricuspid and "flipper" designs, they replaced the mitral valve in 40 dogs. Several kinds of materials were used in these valves, including silastic, lucite, Teflon and arterial homografts. Thrombosis causing valvular obstruction was the chief cause of death in this series, after 5 to 7 days' survival. The most encouraging

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results were achieved with an open, non-rigid quadricuspid valve lying entirely within the left ventricle.

McGovern (1961) used a quadricuspid silastic prosthesis with very similar results to those achieved by others using cusp type valves.

CONCLUSIONS.

The experimental results obtained with the flap type valve prostheses were very disappointing. In the few dogs which survived the initial severe thrombosis, the durability of these valves was very dubious. Haemodynamically they appeared to be satisfactory. In those valves incorporating artificial chordae tendineae the difficulties of insertion rendered valve replacement more of an exercise in technique than a practical procedure.

(b) BALL VALVES.

Hufnagel's excellent work on the aortic valve led to the development and general acceptance of the ball type prosthesis as an intracardiac valvular prosthesis (Hufnagel et al, 1954; Hufnagel et al, 1958). Attempts were made in his laboratories to reconstruct the aortic valve and, while many experiments showed early promise, the late results were not good enough for clinical application. Other attempts were made to replace the aortic valve with homologous aortic or pulmonary valves and the late results were less satisfactory than had been hoped. Reconstruction of valves with segments of pericardium, veins, arteries or a combination

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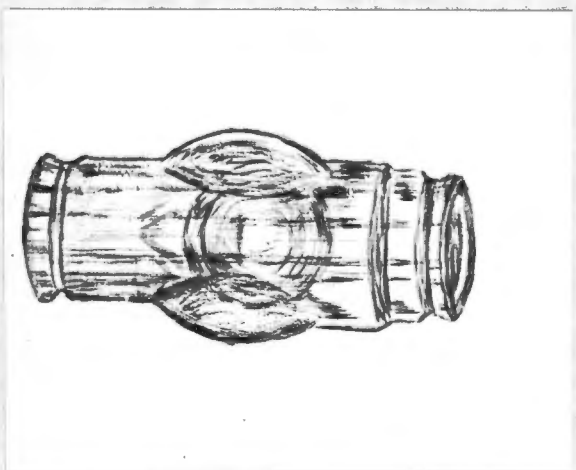
of these substances also proved disappointing. Consequently, in 1944, these workers commenced experimental work to develop a plastic prosthesis. It was only in 1958 that Hufnagel was able to report the successful application of the aortic ball valve. This prosthesis consisted of an inlet, a chamber containing the ball and an outlet (Fig. 6). The entire valve was moulded in a

Fig. 6.



Drawing of aortic ball valve.
(Hufnagel et al, 1958).

single unit, so that the inner surface was extremely smooth without seams. The design of the chamber guided the ball from the seat to the valve stop in an essentially straight line.

Many variations of the ball type prosthesis have been designed since and used experimentally to replace the mitral valve. As early as 1957, Kernan et al described the first caged ball valve, (Fig. 7). This comprised a Teflon shell housing a solid metacrylate sphere 15.5 mm in diameter. The prosthesis was secured by means of a purse-string suture through the mitral annulus, and tied into a groove in the shell. Placed in the mitral ring in 25 dogs, the valve

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proved to be haemodynamically adequate but all the animals died within 21 days except one, which survived 4 months. Extrusion of the ball or displacement of the valve caused 7 deaths; thrombosis occurred in 6 animals - in one the valve was occluded by thrombus and in the others the thrombus was found on the purse-string suture - resulting in fatal emboli.

Fig. 7.

Drawing of caged ball valve, comprising a Teflon shell housing a solid metacrylate sphere. This prosthesis was secured by means of a purse-string suture through the mitral annulus which was tied in the groove at the top of the shell. (Kernan et al, 1957).

Experimenting with various types of ball valves constructed of different materials, Ellis et al (1958) reported that a lucite ball valve and a Teflon valve with a free-floating disc on a central spindle had proved the most suitable for further evaluation.

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Of the lo dogs in this study, only 3 survived operation, the longest survival being 6 days. On necropsy in the survivor, the entire mitral orifice was found to be occluded by thrombus.

Continuing their studies, rings without the valve mechanism were inserted in the canine atrium, different materials being used. Lucite and Teflon rings led to thrombosis whereas Silastic became loose and also produced thrombus formation. Ivalon became completely fixed and was eventually covered with an endothelial-like surface and no obvious thrombus formed on ivalon.

It was through the efforts and excellent experimental work of Starr and his associates that the caged ball valve became widely used for mitral replacement (Starr, 1960; Starr et al, 1960). While experimenting with flap valves, Starr noticed that thrombus developed on the atrial side of the suture line in all cases. During the first few days following operation this thrombus extended to cover the valve ring, whether made from Teflon, Lucite or stainless steel, and eventually it interfered with the function of the flaps. Attention was therefore directed towards the development of a total replacement prosthesis, the function of which would be independent of a complex subvalvular mechanism, and which would not require extensive adjustment in the operating room or surgery more extensive than simple suture to the mitral annulus. They also aimed at the development of a prosthesis not dependent upon the continued flexibility of plastic materials for proper long-term function. It was concluded that a ball valve was best suited.

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They therefore constructed a ball valve which consisted of a rigid Lucite cage, a Silastic ball and a Teflon cloth ring (used for fixation) (Fig. 8). This, the first model of the Starr-Edwards mitral prosthesis, was tested in 7 dogs. It was found that the ball valve was well tolerated in the left ventricle of the normal canine heart and that no extra systoles occurred as a result of infringement of the cage on the ventricular muscle.

Fig. 8.

Drawing of a ball-in-cage valve comprising a rigid Lucite cage, a Silastic ball and a Teflon cloth fixation ring. (Starr et al, 1960).

Although only 2 animals survived longer than a week, the immediate results were encouraging. Of the 2 survivors, 1 died on the 17th day due to thrombus, and the other lived more than 3 months. Examination of the animals which had died from causes other than thrombus (e.g. haemorrhage, pneumonia, sepsis) revealed that there was thrombus on the atrial aspect of the valve ring in 3 cases, but no thrombus on the ball or cage, situated in the ventricle.

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In an effort to prevent thrombosis on the atrial side of the fixation ring, the valve was modified to incorporate a Silastic shield (Starr et al, 1961). With this design, 26 experiments were performed. Necropsy on animals which died within 3 weeks of surgery revealed no thrombus. Thrombosis did occur after 3 weeks but occlusion of the orifice was found in only 1 case.

Gross et al (1963) experimented with a ball valve of their own design, a Starr-Edwards valve and a lens type valve. Using these three prostheses, they obtained similar results. Only 3 dogs lived longer than a month after surgery. This group of workers also noticed the absence of thrombus originating on the ventricular aspect of the prosthesis and suture ring. Fibrin formation commenced in the areas of contact between prosthesis and atrial endocardium, the thrombus extending then over the entire flange, through the orifice and eventually occluding the orifice. By diminishing the bulk of the atrial flange, they were able to reduce the extent of the inevitable thrombus and to prevent occlusion of the valve orifice.

In an attempt to reduce the extent of obstruction to atrial outflow, Cartwright and his colleagues (1964) developed a Titanium double-caged orifice ball valve for mitral replacement (Fig. 9). The advantage envisaged was that the valve would be open at both ends. Of the 16 dogs subjected to replacement, 2 did not survive the operation. Ten dogs survived for 21 days, 3 were sacrificed at 21 days and 1 survived for 18 months. Late deaths were due to

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embolisation and infection. All 3 animals sacrificed revealed thrombus in the usually encountered site: on the atrial aspect of the valve, on its fabric rim and with circumferential encroachment at the base of the small upstream struts.

Fig. 9.

Drawing of double-caged orifice ball valve. (Cartwright et al, 1964).

CONCLUSIONS.

From these results it is apparent that the ball valve is durable, and is satisfactory from the haemodynamic point of view. However, thrombus formation still presents a major obstacle to long-term survival.

B. CLINICAL.

Due to the pressing need for total mitral valve replacement in humans, and with the knowledge that the clotting mechanism of the dog is different from that of man, many types of prostheses were

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introduced clinically before being properly evaluated in the research laboratory.

(a) FLAP VALVES.

(1) Flap valves incorporating artificial chordae tendineae:

Despite the poor results obtained in animals, Braunwald et al (1960) inserted their flexible polyurethane valve with its Teflon tape "chordae" in 5 patients. There were 3 operative deaths, due to technical failure. One patient survived for 14 hours and the other for 3 months. At autopsy of the latter patient, no thrombus was found on the valve, which was covered with a thin layer of fibrin but had remained pliable and mobile.

Using the same type of valve, Kay et al (1961) could not improve on these results with their Teflon sleeve valve with artificial chordae tendineae. None of their 5 patients survived.

(2) Flap valves without artificial chordae tendineae:

(i) Monocusp Flap Valves:-

Ellis (1960) reported the clinical use of monocusp Mylar valves covered with thin, knitted Teflon fabric, in 4 patients. One died on the night following operation and another on the 5th post-operative day. In both cases the valve seemed to function satisfactorily during the survival period and death appeared to be due to other factors. Another of the survivors died after a month, due to heart failure. Autopsy revealed no ingrowth of tissue into the ivalon ring. The valve was thus displaced into the atrium. The remaining patient in the series died after 1½ months, due to

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subacute bacterial endocarditis. On examination post mortem, there was a thick layer of fibrin over the valve which seemed to have interfered with its function.

Still later, Ellis et al (1963) reported 19 cases of mitral valve replacement using a modification of this prosthesis. The ring was constructed from laminated Mylar banded with Schjelband 100. The flexible cusp, likewise, was made from Mylar and was covered with knitted Teflon fabric. Outside the Mylar ring was sutured knitted Teflon cloth. In this series there was no evidence of structural failure. Only 1 patient was reported to have died, after 6 months, as a result of embolisation.

(ii) Multicusp Flap Valves:-

Long et al (1960) reported the use of a Silastic tricuspid prosthesis in 1 patient, who died 9 days after operation. Thrombus (originating at the junction of endocardium and the prosthesis) was found both on the atrial and on the ventricular surfaces of the valve.

CONCLUSIONS.

The clinical results suggested that there was no place for a prosthetic mitral valve with chordae in clinical cardiac surgery. The results obtained with the monocusp valve was promising in that it gave satisfactory haemodynamic results, but its durability is still suspect. Although Ellis et al (1963) report a very low incidence of emboli post-operatively, as compared with his series in which a ball valve was used, a longer post-operative interval is necessary for proper evaluation of the results.

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(b) BALL VALVES.

If Starr's experimental results using the Starr-Edwards caged ball valve had been encouraging (1960), his initial clinical results were even more so (Starr et al, 1961). In the 8 patients constituting the first series reported, 6 survived the operative procedure of mitral valve replacement; the 2 deaths were unrelated to the prosthesis itself. The first 2 patients undergoing this procedure were free of cardiac symptoms and back at work shortly after operation. No evidence of emboli was reported. However, the author was guarded in his conclusions and suggested that mitral valve replacement was indicated only in the severely incapacitated patient with operative findings of a hopelessly damaged valve not amenable to any plastic repair.

Effler was far more enthusiastic (1962). Of the 22 patients in whom he replaced the mitral valve with the Starr-Edwards prosthesis, only 6 died within 6 weeks and in only 1 was death attributable to emboli. Unlike Starr, he used no anticoagulants in these patients. This led Effler to write "on the basis of personal experience, we have rejected virtually every method of annuloplasty and valvuloplasty that was employed during the preceding six or seven years. As stated before, the initial success with the Starr-Edwards valve has been promising and at the moment we consider it the treatment of choice for the patient who needs surgical relief of mitral valve incompetency." However, he added "there is little doubt that this best form of surgical treatment does not constitute the ultimate, but is only another phase in the continued search for better surgical treatment for mitral

insufficiency."

The mitral valve was replaced with the Starr-Edwards valve in 37 patients at the Mayo Clinic (Ellis et al, 1963), and 4 of the late deaths were due to embolisation.

Lillehei (1963) reported 7 survivors in his series of 10 replacements. Two patients who were not receiving anticoagulants experienced late embolic complications and he advised the routine use of anticoagulant therapy to prevent this complication.

Magovern and Cromie (1963) developed a sutureless prosthetic heart valve in an attempt to reduce the operative time. The valve mechanism is a Silastic ball in a stainless steel open-end cage. Of the 3 patients in whom the mitral valve was replaced with this prosthesis, 1 died after 6 weeks. At autopsy, massive right cerebral vascular haemorrhage was found; there was no evidence of embolism. It was felt that the incidence of thrombosis should be reduced through the elimination of sutures and cloth, which reduced the nidus for thrombus formation.

A large number of long-term results have now been reported (Björk and Mahers, 1964; Barnard et al, 1965; Effler et al, 1965; Herr et al, 1965; Lillehei et al, 1965; Dubost et al, 1965). It is evident from these that the ball valve has proved satisfactory in all respects except thrombosis complicated by emboli. The manner of presentation of this complication is either by massive thrombus occluding the valve orifice, or by systemic emboli. The former fortunately occurs rarely (Garamella et al, 1964; Davila, 1965),

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but the latter is much more common.

Herr et al (1965) reported a 42% incidence of emboli in 65 patients in whom the mitral valve had been replaced by Starr and his associates. Björk and his colleagues (1965) report an incidence of approximately 50% using the Starr-Edwards prosthesis, and the use of anticoagulants did not appear to make any appreciable difference to these results. Effler et al (1965) report a 22% incidence only in 97 patients with the Starr-Edwards valve, without the routine use of anticoagulants.

An additional disadvantage of the Starr-Edwards prosthesis is the large cage which projects into the left ventricle. Most authors do not feel that this causes any problems (Herr et al, 1965), but others express the fear that as a result of the pounding of the cage against the septum, an irritable focus may result in ventricular fibrillation (Byron, 1965). It has been suggested that the large cage projecting into a small left ventricle will produce outflow obstruction (Byron, 1965; Wada, 1965).

As a result of these objections, many attempts have been made to reduce the bulky intraventricular cage size. Melrose et al (1964) describe the construction of a polypropylene self-retaining ball valve. Lillehei et al (1965) evolved a caged meniscus valve in which the meniscus is free-floating and semi-rigid, rotating freely to distribute wear (Fig. 10). Hufnagel and Auvard (1965) developed a discoid valve (Fig. 11).

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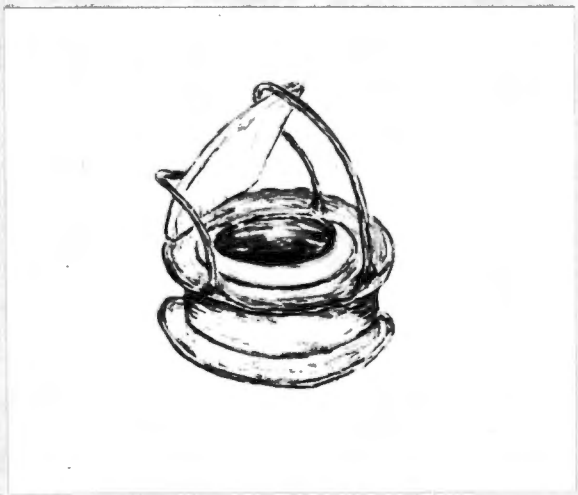
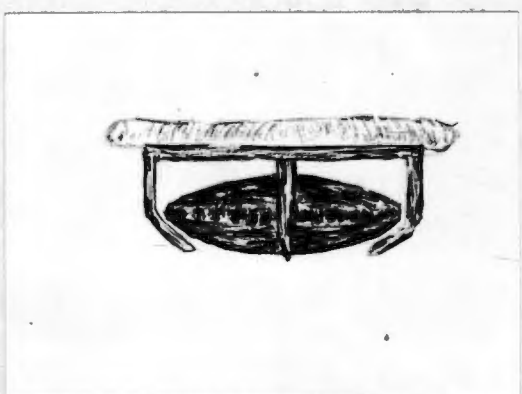
Fig. 10



Drawing of caged meniscus valve. (Lillehei et al, 1965).

Fig. 11.



Drawing of discoid valve. (Hufnagel and Auvard, 1965-).

CONCLUSIONS.

It may be concluded that the ball valve fulfils most of the criteria of an ideal mitral prosthesis, notwithstanding the fact that it has been shown to be stenotic. Thrombus formation, however, remains a formidable problem.

TOTAL MITRAL VALVE REPLACEMENT WITH AUTOGENOUS OR HOMOLOGOUS TISSUE GRAFTS.

In an endeavour to achieve better results following mitral valve replacement, various tissues have been used experimentally and clinically. These tissues may be taken from the subject itself (e.g. vein, artery, pericardium) - autogenous grafts, or from another member of the same species - homografts.

(a) AUTOGENOUS GRAFTS.

Experimental:-

Autogenous pericardium has chiefly been used since Wilson's first report in 1930. Progressive contraction and loss of pliability of pericardial grafts placed within the left ventricle has been a uniform observation in the dog and in man, when a vascular pedicle is maintained (Lan et al, 1952; Sauvage et al, 1961). When autogenous pericardium was used as valve cusps it did not undergo any marked degenerative changes (Bakst et al, 1958; Sauvage et al, 1962).

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In a more recently published article, Frater et al (1965) noted that degenerative changes were always evident at post mortem examination two or more months after surgery.

These experiments, however, did show that it is possible to construct prosthetic cusps and chordal sheets which function normally, without copying the removed natural tissue. Furthermore, in direct contrast to the experience with plastic prosthetic valves, massive thrombosis with valve obstruction or emboli did not constitute any problem despite the fact that anticoagulants were not used.

Clinical:-

Using autogenous grafts to restore the function of destroyed mitral valve cusps in human beings, rather more favourable and different results were obtained (Sauvage et al, 1962; Frater et al, 1965). Good valve function was maintained for more than two years. Autografts available for pathological examination showed minimal fibrin formation and no micro-organisms in early specimens. Later specimens showed minimal thickening with preservation of pliability.

On the other hand, a disappointing feature of these studies is the early recurrence of murmurs in patients whose lesion appeared completely corrected during the first post-operative month.

Although the augmentation or repair of mitral leaflets using autogenous pericardium appears to be promising, total mitral valve

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replacement by this means is a formidable procedure associated with a high failure rate.

After careful study of the normal mitral valve, Van der Spuy (1964) developed a completely anatomical entire mitral valve from autogenous tissues. This is made from autogenous pericardium, previously cleared of mediastinal pleura and fat, using "cusp plates". The completed valve closely resembles the normal mitral valve, having two sets of chordae tendineae (fig. 12). The common

Fig. 12.

Drawing of valve made from autogenous pericardium. The valve closely resembles the normal mitral valve and has two sets of "chordae tendineae". (Van der Spuy, 1964).

stem of each set of chordae is embedded in a papillary muscle. The oval base of the valve is sutured to the ring of the excised mitral valve. No details of the experimental and clinical results are as yet available.

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CONCLUSIONS.

It seems clear that autogenous tissue can be used to replace part or all of the mitral valve, and that embolic manifestations are markedly less than when artificial prostheses are used. The retention of adequate function of the cusps or valve made from autogenous tissue after a few years must still be proved. A major disadvantage is the great technical difficulty posed by total mitral valve replacement by this means, resulting in a high operative mortality rate.

(b) HOMOGRAFTS.

Although organ transplantation is carried out in many centres today, experimentally and clinically, much has still to be learnt before routine clinical use can be contemplated. The concept of the replacement of the diseased mitral valve with a healthy homograft seems to be the ideal treatment, but the fate of these grafts is not yet known. Furthermore, due to its more complex anatomical components, the mitral area renders itself much less favourably to this procedure than for example the aortic area. As a result, much of the work which is being done in the field of homografts constitutes the study of valves other than the mitral, the aortic valve having received the most attention.

Experimental:-

Hufnagel (1951) reported that homologous aortic valves failed to function normally when placed in the descending aorta of dogs.

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The opposite view was expressed by Murray (1956), however, who showed that these grafts not only survived but also functioned well for periods up to 9½ months. It was also demonstrated that both fresh and preserved homologous aortic valves thus inserted would become inactive unless persistent aortic incompetence was produced.

Generally speaking, the fate of intracardiac homologous grafts in dogs has been unpredictable. Using different valves in different positions, some reported that the leaflets become thickened and retracted (Hiembecker et al, 1962); the valves become incapable of normal function (Litwak et al, 1952; Pollock and Thomas, 1956).

The homologous aortic valve has also been used for total mitral replacement (Murray, 1956). It was placed in the mitral annulus in an inverted position and two tails of aorta were used as "chordae", being inserted in the papillary muscles. Survivors have been reported at 9½ months (Murray, 1956) and at 5 months (Willman et al, 1960). Necropsy revealed the valves to be covered with vegetations, the leaflets contracted and distorted. Microscopy showed evidence of homograft rejection and signs of subacute bacterial endocarditis. Altering the technique, the valve being anchored to the ventricular myocardium, the results were even worse: no survivors were reported (Heimbecker et al, 1962).

It has been said that it is technically possible to transplant the mitral valve from one dog to another (McKenzie et al, 1963).

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These authors had 1 animal surviving 7½ months after this operation. Good healing of such homografts has been shown, both of annulus and of the papillary muscles. Another encouraging feature is that at necropsy, 5 months after insertion, the grafts have been observed to be pliable and relatively normal in appearance.

Clinical:-

The clinical results of the use of homologous grafts in the aortic area are very encouraging. Murray (1956) reported the first such success, placing the homograft in the descending aorta, and subsequently reported 3 patients still alive after 4½, 2½ and ½ years (Murray, 1960). Still later, Kerwin et al (1962) wrote that the patient on whom Murray had operated in 1956 was still alive after 6½ years. The same authors also achieved 5 successes in 9 operations.

Barratt-Boyes' results with homograft aortic valve replacement (1964) compares favourably with those following prosthetic replacement of this valve. He also described the successful application of a "graft storage bank". The homograft was obtained by the pathologist either under fully sterile conditions, or unsterile, within 15 hours of death. Valves were taken from donors up to the age of 55 years. When they were removed under unsterile conditions, the valves were immediately sterilised using betapropiolactate and were placed in a nutrient medium to which penicillinand streptomycin had been added, and were stored at 4°C for up to a week before freeze-drying. The valves were cultured before being placed in the

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medium and again on removal, before freeze-drying. If the culture was positive they were discarded. After freeze-drying, the exterior of a sealed glass vacuum tube was sterilised in an ethylene oxide gas chamber at body temperature. Just before use, these freeze-dried valves were reconstituted by placing them in distilled water for 30 minutes and then in isotonic saline. Of the 44 patients who received these aortic homografts, 41 have normally functioning aortic valves up to 15 months after surgery. Significant morbidity was limited to post-operative endocarditis, rapidly cured by a single course of antibiotics, in one case, and permanent complete heart block in another. Two of these homografts have been examined at autopsy, 2 and 4½ months after insertion, and the architecture of the cusps was normal in both cases.

In the field of mitral homograft replacement the reports are scanty and the results are not encouraging. Murray (1956) reported one case but no details as to the patient's course have been published. The only other report is one by Hiembecker et al (1962) and their patient died 1 month after operation. At autopsy the leaflets were pliable and functioning.

Both Barratt-Boyes (1965) and Ross (1965) have also had limited clinical experience with mitral homografts in human-beings. Here again, however, technical difficulties resulted in a prohibitive surgical mortality.

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CONCLUSIONS.

The results with homograft aortic valve replacement are most rewarding, suggesting that human rejection responses are not very active in this area. In the mitral valve area it is likely that similar results will be achieved, but the technical difficulties are far greater and must still be overcome.

THE PREVENTION OF THROMBO-EMBOLISM FOLLOWING THE INSERTION OF MITRAL PROSTHESES.

From the preceding chapters it is clear that an artificial prosthetic valve is the only satisfactory means for total replacement of the mitral valve at present. It is also apparent that thrombosis is a constant threat whenever these prostheses are employed, regardless of their construction.

The mechanism of the initiation of thrombosis is unknown. Sawyer and his associates (1960) have postulated for many years that the injury of a vessel wall changes the normal negative charge on the endothelium (relative to the surrounding tissue) to a positive one. The blood cells, normally being negatively charged, are repelled by normal endothelium but are attracted to injured endothelium. This seems a feasible explanation for the initiation of thrombosis following mitral valve replacement.

The factors which determine the propogation of the thrombus are also unknown. It is likely that both flow characteristics and the properties of the valve surface influence this effect. Alterations in the electrical charges may also be implicated (Frater and Ellis, 1960).

Theoretically, thrombosis may be reduced or prevented if fibrin deposition can be prevented, or if fibrin deposition can be digested once it has occurred, by the use of drugs or electrical charges.

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EXPERIMENTAL SURVEY.

(a) PREVENTION OF FIBRIN FORMATION.

(i) Electric Charges:-

In order to induce a negative charge on the surface of valves, Frater and Ellis (1960) had them gold-plated. The results of this study suggest that this step did not influence the formation of thrombus. A similar conclusion was reached by Kolff et al (1960).

(ii) Systemic Drug Therapy:-

The systemic use of heparin (Frater and Ellis, 1960; Malowney et al, 1965) and of other anticoagulants (Starr, 1961; Clark and Muller, 1962; Gross et al, 1963) resulted in an increased incidence of bleeding post-operatively and did not prevent thrombosis. Other workers found that the administration of dicoumaral appeared to prolong survival and to diminish deposition of thrombus (Doumanion et al, 1961; Malowney et al, 1965).

(iii) Graphite-benzalkonium-heparin coated Prosthesis:-

As a result of the poor experimental results of mitral valve replacement in their laboratories, Gott et al (1961) attempted to find a more satisfactory material for the prosthetic valve. They believed that a severe test of thrombus formation would be the insertion of the valve in the inferior vena cava of dogs. Uncoated plastic rings, silicone-coated methyl methacryalate rings, graphite coated methyl methacryalate rings with brush or dip application, and graphite coated methyl methacryalate rings with electrical charges, were used in their investigation.

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With the exception of rings constructed from Kel F and high density polyethelene, all rings were severely thrombosed within 2 hours. A silicone coating on methyl methacryalate rings reduced the thrombus formation on the prosthesis significantly. All rings of methyl methacryalate coated with conductive graphite (by a dipping process) were virtually free of thrombus after 2 hours. Application of a negative charge to the graphite surface did not alter these results, although the application of a positive charge produced a severe thrombosis within 1 hour.

After promising results achieved with a pulmonary artery valve prosthesis (only 3 of 25 animals dying as a result of thrombosis), these workers' results in the mitral area were even more striking (Gott et al, 1962). In 1964, they reported the results of total mitral valve replacement in dogs using a hinged-leaflet mitral prosthesis with graphite-benzalkonium-heparin coating. The number of dogs in this series is not mentioned, but 70% survived for longer than 3 months. Necropsy in 1 animal which died after 3 months due to disruption of the prosthetic-annular suture line showed no significant thrombus on the suture line or prosthesis.

(b) <u>THE DIGESTION OF FIBRIN DEPOSITS ON PROSTHESIS</u>:

Kolff et al (1960) used fibrinolysin after insertion of the prosthetic patches he was testing in the left atrium of dogs. It was his conclusion that this was undoubtedly helpful in the prevention of thrombosis.

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Frater and Ellis (1960) used thrombolysin and "Varizyme" in doses suggested by the manufacturers for a similar investigation. In all the dogs studied thrombus formation on the prosthesis was not prevented.

CLINICAL SURVEY.

The value of long-term anticoagulation therapy has not been proven. An impressive number of bleeding complications of serious degree resulted (haemopericardium, haemothorax and gastro-intestinal bleeding) and tempered the enthusiasm of some workers for this procedure (Effler et al, 1965). Others again recommend the use of anticoagulants (Lillehei, 1963).

Davila (1965) reviewed the incidence of late deaths following total mitral valve replacement in anticoagulated and non-anticoagulated patients. In the former group (600) there was an incidence of 8.5% late deaths and in the latter group (200) the incidence was 13.5%. These results indicate that fatal thrombo-embolism is seen somewhat more frequently in the non-anticoagulated group.

Most authors appear to agree that, despite its limitations, anticoagulant therapy should be used after mitral replacement in

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all cases. In this connection, the findings of Carter and his associates (1958) - that there is an increased incidence of emboli within 6 weeks of discontinuing the administration of anticoagulants - should be borne in mind. Anticoagulant therapy should be tailed off gradually to prevent the occurrence of this rebound phenomenon.

THE UNIVERSITY OF CAPE TOWN MITRAL VALVE PROSTHESIS.

THE UNIVERSITY OF CAPE TOWN (U.C.T.) MITRAL VALVE PROSTHESIS.

EXPERIMENTAL REVIEW.

Stimulated by the success of others, this University started a project to develop a mitral prosthesis. A ball valve of the type developed and used, experimentally and clinically, by Starr was designed. It was attempted to provide maximal flow with the smallest possible ring and cage.

A stainless steel ring and cage was used with a Silastic ball (Fig. 13). The ring was covered with ivalon, to hold the sutures and permit tissue ingrowth. Insertion into the canine heart was possible but resulted in death within an hour, due to ventricular fibrillation. Necropsy revealed significant trauma to the intraventricular septum, suggesting that the cage was too large for the canine ventricle, causing damage to the conduction system and giving rise to fibrillation.

Thus it was decided to construct a ball valve without a cage. Although extensive tests in a pulse duplicator were encouraging, experimental trial again resulted in the death of all dogs within 24 hours - now thought to be due to ventricular outflow obstruction caused by the round ball.

It was then realised that, in this type of valve, the lower half of the ball served no real purpose. By removing the lower

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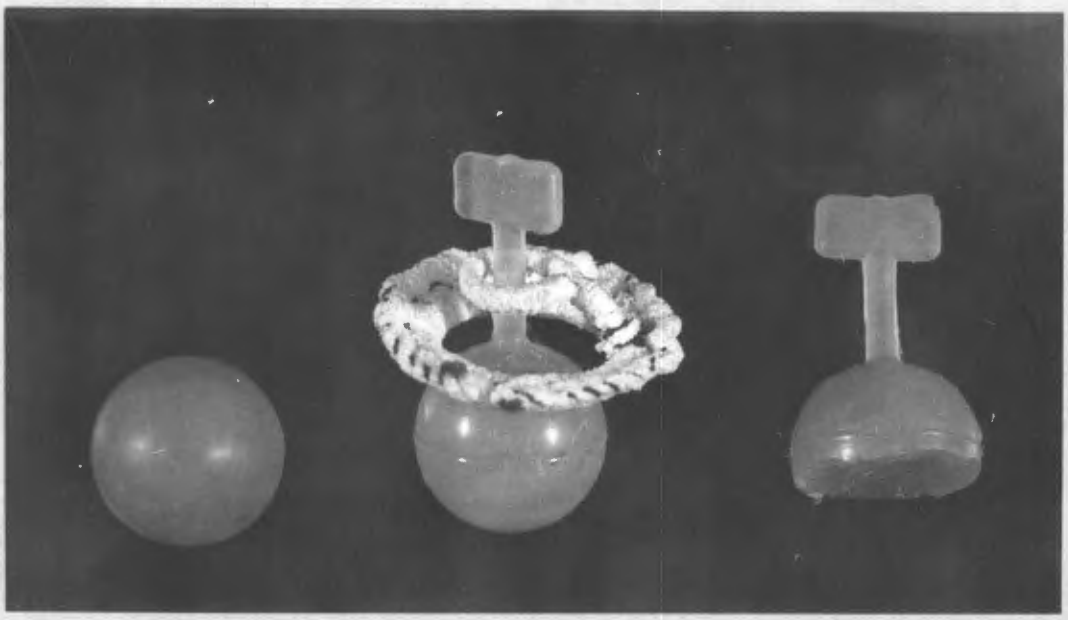
Fig. 13.

The ball-in-cage valve used in mitral valve replacement experiments at the University of Cape Town. The ring and cage are stainless steel and the ball is made from Silastic.

half of the ball (producing a lens shape) it would still close the valve and the possibility of trauma to the septum and of outflow obstruction would be minimised (Fig. 14). It was also calculated that an increase in radius of the curvature of the spherical surface meeting the valve ring would allow the use of a thinner lens-shaped ball, eliminating the danger of impacting the ball into the ring.

Fig. 14.



This photograph illustrates the experimental development of the lenticular mitral prosthesis. The lower half of the spherical ball is removed and a retaining guide rod introduced, eliminating the cage and minimising the dangers of trauma to the ventricular septum, outflow obstruction and the impacting of the ball into the ring.

THE VARIOUS MODIFICATIONS OF THE U.C.T. MITRAL PROSTHESIS USED CLINICALLY.

MARK I (Fig. 15).

First used clinically in May 1962, this prosthesis consisted of a stainless steel ring to which was attached a suspension bar. The ring and bar were ivalon-coated. The ring was pierced with many holes and, before insertion, was covered with compressed polyvinyl sponge. This allowed suture into the mitral annulus. The mobile part of the prosthesis was made from Silastic, a plastic-rubber combination, and consisted of a lens-shaped ball with a stem and a cross-bar.

When assembled, the cross-bar was passed through the ring of the suspension arm. In the open position, the ball lay about 1/4" below the ring, suspended by its cross-bar on the arm of the ring. To close, the ball was guided by its stem.

Fig. 15.

The Mark I U.C.T. Lenticular Mitral Prosthesis.

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Modifications of these features were suggested in an attempt to reduce the incidence of post-operative emboli experienced clinically, and to allow better valve action at faster heart rates.

MARK II. (Fig. 16).

Fig. 16.

The Mark II U.C.T. Lenticular Mitral prosthesis, with steel seat and lighter mobile unit.

The mobile portion of the valve had a smaller mass and closed against a stainless steel surface. The steel ring incorporated a double-grooved outer rim. In the upper groove Dacron cloth was sutured, just before insertion, providing a suture ring.

MARK III. (Fig. 17)

Further modification was designed to facilitate intra- or subannular insertion of the prosthesis, the difference being that the steel ring was decreased in depth and only one groove was provided for the Dacron suture ring (Fig. 18).

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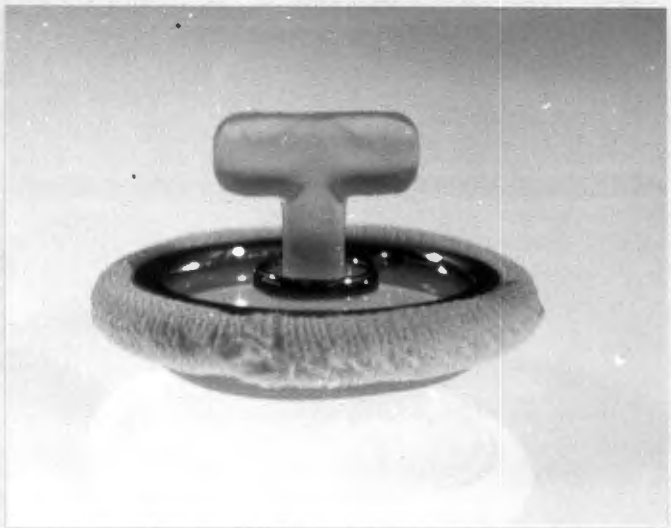
Fig. 17.



The Mark III U.C.T. lenticular Mitral Prosthesis.

Fig. 18.

The stainless steel rings of the Mark II and Mark III U.C.T. lentirubar mitral prostheses showing (left) the single-grooved Mark III and (right) the double-grooved Mark II.

CLINICAL REVIEW.

The University of Cape Town (U.C.T.) lenticular mitral prosthesis, Mark I, was introduced clinically at an operation performed on May 14, 1962 (Barnard et al, 1962). As with other mitral prostheses, the first reports were encouraging when, a little later, the first 6 cases were described (Barnard et al, 1963).

Initially, the prosthesis was sutured on the ventricular side of the mitral annulus. The sutures were tied on the atrial side over an ivalon ring, to decrease the possibility of the stitches pulling through. The return to normal cardiac function was remarkable up to a period of 5 months after surgery. One patient developed a hemiplegia 5 months post-operatively as a result of embolus. The authors concluded that the dangers of embolisation are always present in patients with rheumatic mitral valve disease, and atrial fibrillation, even using anticoagulants. They stressed the importance of further study before the long-term value of the prosthesis could be assessed.

In their next report, Barnard and his colleagues confirmed this advice (1965). They discussed the long-term results of 18 patients in whom the prosthetic valve had been used. There were only 2 hospital deaths, one from a blocked endotracheal tube and the other due to air embolism, indicating the low operative mortality associated with this procedure, in spite of the fact

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that most of these patients were from the functional Class IV group. Of the 7 cases followed up for a year or longer after surgery, 6 were living normal lives.

The durability of this valve was proved. Its haemodynamic effieiency was confirmed by catheter studies and cine-angiocardiography. Nine patients (2 of whom had infective endocarditis) had small transient cerebral episodes, presumably due to minute emboli. Embolic manifestations occurred at any time from 3 weeks to 18 months after surgery.

Of the 51 patients who, at time of writing, had undergone total mitral valve replacement with the U.C.T. prosthesis since its introduction in 1962, 49 have been followed up for at least 3 months post-operatively (Ferguson, 1965). The Mark I and Mark II valves were used in the majority, 6 being placed in the sub-annular position, with an atrial ring of plastic material, and the remainder in the supra-annular position. More recently, the Mark III valve was used in 3 patients in the intra-annular position.

In spite of the variation in valve design and the difference in the site of insertion, the incidence of emboli encountered post-operatively has been alarming. Embolic manifestations occurred from within 10 days of surgery up to a period of almost 2 years or more later. Embolus was the direct cause of death in 13 of the 14 patients in this series who died after leaving hospital. A further 9 were left with severe neurological symptoms after an embolic episode, and in 15 patients there was no permanent disability. Only 11 of the 51 patients have experienced no signs of embolus.

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HAEMODYNAMIC STUDIES.

Eleven of the 12 patients who have survived a year or more after surgery have been studied by cardiac catheterisation and cine-angiocardiography (Beck et al, 1965). All showed a marked improvement in mitral valve function and in every case, judged by cine-angiocardiography, the valve was competent.

At rest, the mean diastolic pressure gradient varied between 1.2 and 12 mm.Hg, resembling the findings of mild mitral stenosis without incompetence. The pulmonary arterial pressure had fallen in all but one patient. Exercise produced a rise in both left atrial and pulmonary arterial pressures, as might be expected in patients with mild mitral stenosis. It was thought that the inertia of the mobile part of the prosthesis might result in less satisfactory function at faster heart rates, but the inaccuracy of formulae to establish effective valve areas when the gradient is small rendered it impossible to decide whether this was so.

The residual gradient was thought to be due mainly to inadequate orifice size, although a delay in reaching the fully open position may also play a part. Poor ventricular function could also be a cause, and was noted to be present in 3 patients.

In concluding their report, the authors compare the orifice areas of the U.C.T. and the Starr-Edwards prostheses of equivalent external diameter. The former has a distinct advantage, which may account for the slightly smaller gradient present compared with

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the results published using the early Starr-Edwards valve, which has a smaller orifice area.

To date, the results after insertion of the Mark III valve in the intra-annular position appear to be more promising, although long-term follow up is necessary before it can be established whether real improvement has been achieved.

EXPERIMENTS.

EXPERIMENTS.

MATERIALS AND METHODS.

APPARATUS.

The cardiopulmonary bypass apparatus used in these experiments was the helix reservoir bubble oxygenator, as first described by DeWall et al (1956; 1957), with a few modifications.

All the blood lines are of polyvinyl tubing. Latex hose 3/4 inch in diameter is used in the pump heads and a Sigmamotor Pump, Model TM.2, is used for pumping venous blood through the oxygenator and to return arterial blood to the animal. Special highly polished stainless steel connectors are used to join the various plastic components in the circuit. These connectors have no abrupt shoulders or other obstructions, to minimise turbulence.

CIRCUIT.

The components of the oxygenator are connected, as shown in Fig. 19. Blood is drained by gravity from the right atrium into a venous well. Drainage is further assisted and controlled by suction, applied to the venous well. Cardiotomy return blood is drained into another well. These wells are placed close to the operating table, the bottom of the well being approximately 20 inches below the level of the right atrium.

From the venous well, the blood is pumped through the venous circuit into a vertical mixing chamber where it is permeated with

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Fig. 19.

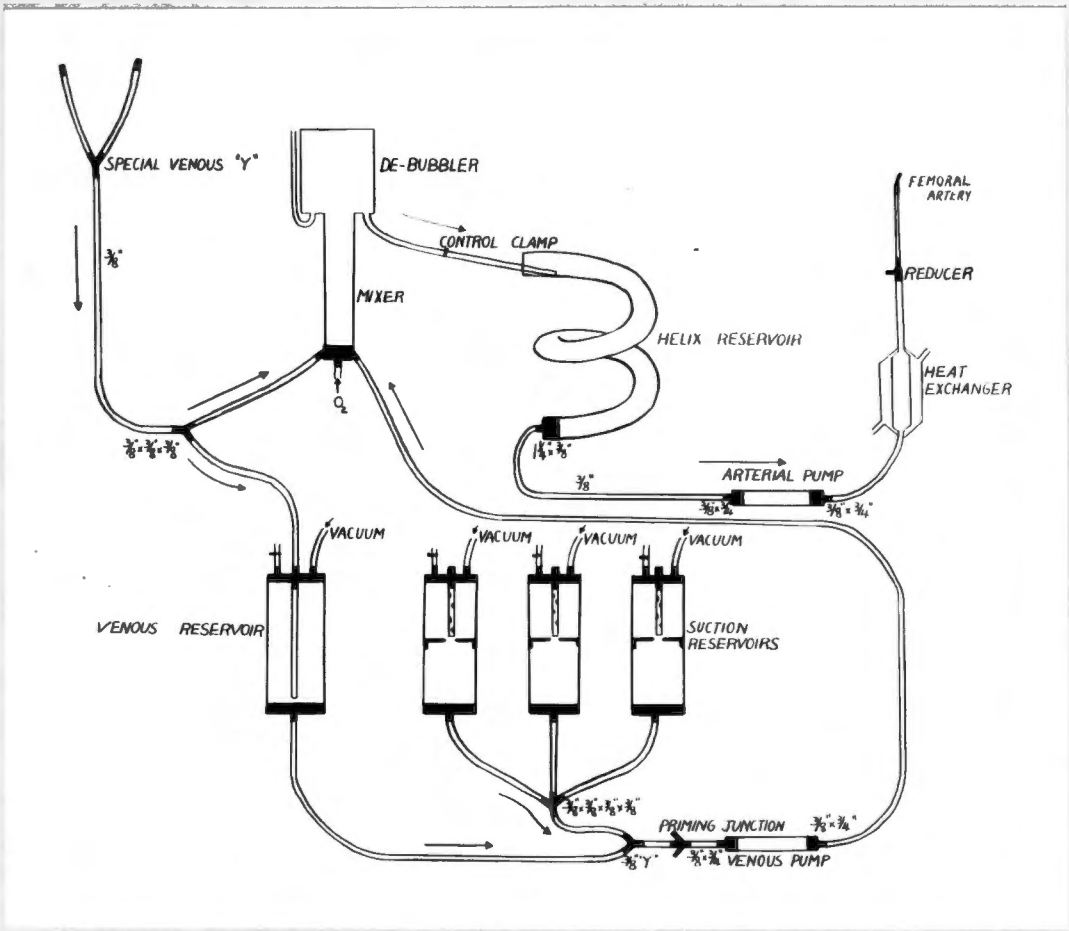

Diagram illustrating the assembly of the components of the DeWall-Lillehei helix reservoir bubble oxygenator.

100% oxygen, by way of an oxygen diffusion plate positioned at the bottom of the mixing chamber.

The blood-oxygen mixture rises in the mixing chamber and overflows into the debubbling can. Debubbling is effected by three antifoamed* stainless steel sponges which are arranged around the perforated top of the mixing tube (Figs. 20a, b, c, d and e), in a Teflon-coated can.

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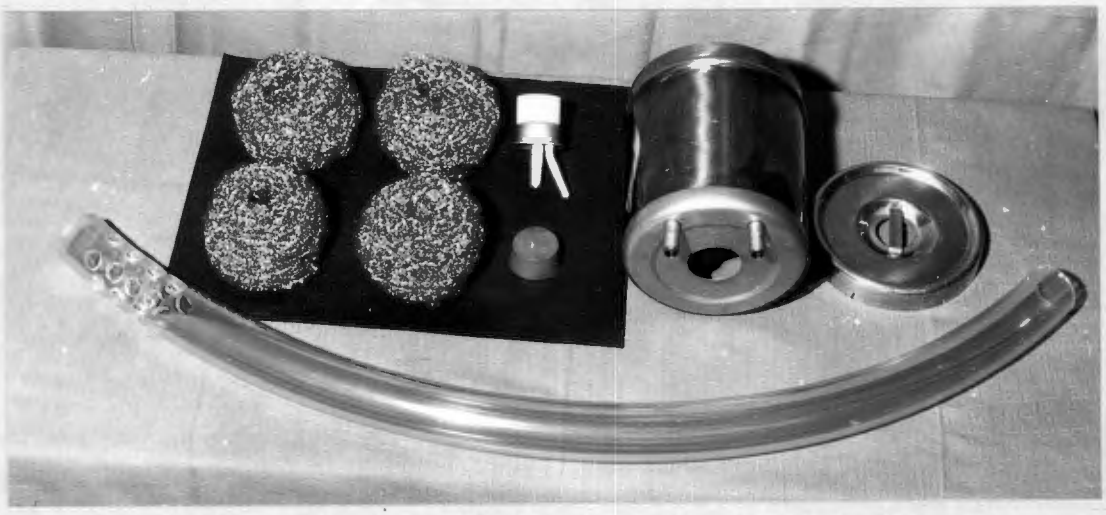
* Antifoam supplied by Dow Corning Corp.
Midland, Michigan, U.S.A.

Fig. 20 a.

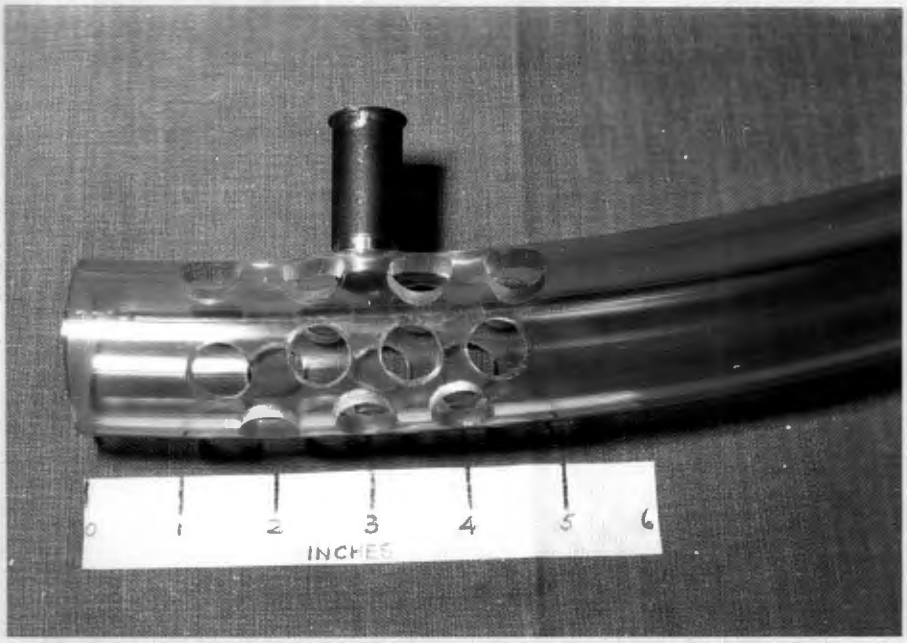


The various unassembled components of the debubbling system.

Fig. 20 b.

Debubbling system: the mixing tube shown after insertion into the bottom of the can. The two peripherally placed outlets can be seen.

Fig. 20 c.



Debubbling system: The top of the Mayon mixing tube showing the placing of the holes, which are made with a specially turned tool (also to be seen in this photograph).

Fig. 20 d.

Debubbling system: The stainless steel sponges have all been placed over the holes in the top of the mixing tube, forming a closely knit barrier through which the oxygenated blood must pass. The bubbles are thus eliminated.

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Fig. 20 e.

Debubbling System: The lidless cannister as seen from the top. The stopper is in place in the end of the mixing tube around which the sponges are arranged.

The debubbling chamber is designed to dissipate the bubbles and to separate the excess oxygen and carbon dioxide from the arterialised blood.

After debubbling, the oxygenated blood empties into a helix which is wound around an aluminium stand (Fig. 21). The helix is made from 1¼ inch internal diameter Mayon tubing, and its length is such that it will accommodate a volume of blood equal to 1 minute's flow plus 400 ml. The helix acts as a reservoir and also removes any free gas remaining in the arterialised blood. The mechanism was fully described by DeWall et al (1956).

Once oxygenated, the blood is pumped through two Benington* heat exchange units where it is cooled or warmed (Fig. 22). This heat exchanger works on the principle that the blood entering is

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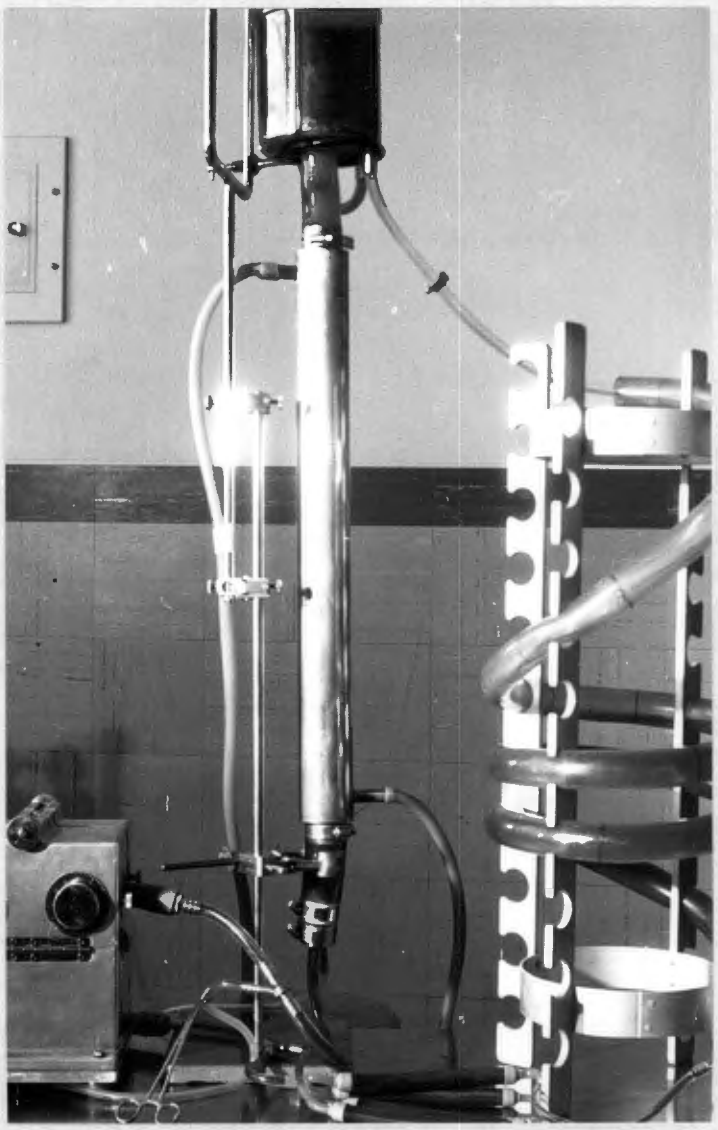
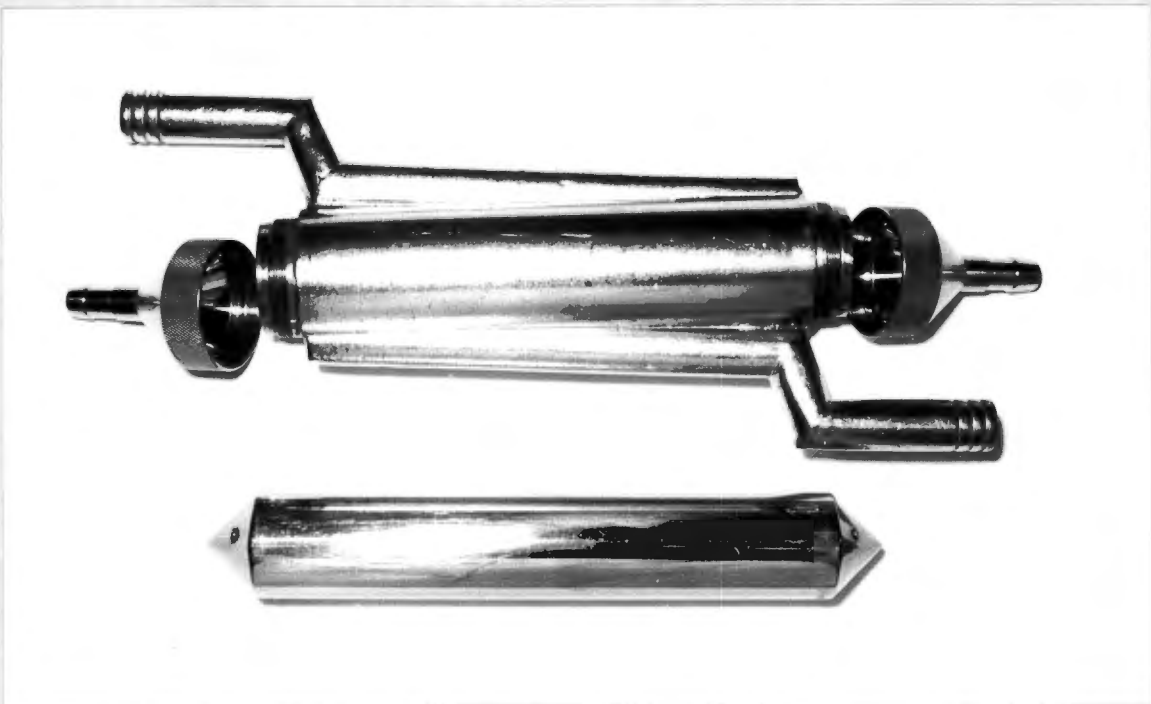
* Benington & Son, Jeppe, Johannesburg.

Fig. 21.



The assembled debubbling system showing the helix wound around an aluminium stand.

Fig. 22.



The Benington heat exchange unit, showing the highly polished inner component.

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spread in a thin film over a highly polished inner component, so coming into contact with the similarly polished inner wall of the jacket carrying the heat exchange fluid. Water from a tank containing melting ice is used for cooling, and warmed water of between 40–45°C for rewarming. The water is pumped through the jacket at a rate of 12 gallons per minute (Barnard et al, 1961).

The rectal and mis-oesophageal temperatures of the animal are recorded during the operation, using an electric Universal

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thermometer. The electrothermometer operates on the thermocouple principle, reads almost instantaneously and is accurate to 0.1°C (Terblanche and Barnard, 1962).

The oxygenated and cooled/warmed blood is returned to the dog through the arterial catheter, in the right common femoral artery.

PRIMING.

On the morning of the experiment, the autoclaved equipment is assembled by a technician, under sterile conditions. The water tanks are connected to the heat exchangers via the water pump. Once the apparatus is completely assembled and in place on a trolley, priming is commenced.

(1) Initial Priming with Saline.

A vacolitre of normal saline is placed in a boiling steriliser for 30 minutes. The contents of the vacolitre are then poured into the top end of the helix and the hot saline flows through the helix and filter. Once the latter has filled, a clamp is applied to the arterial line distal to the filter. Filling is then continued until the helix contains approximately 800 ml. of fluid, when a second clamp is applied to the arterial line proximal to the filter. The saline in the system is inspected for bubbles. Any bubbles present are dislodged by tapping the helix and filter forcefully with a patella hammer. Once the helix and filter have been cleared of bubbles, the clamps on the arterial line are removed

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and the saline is allowed to flow slowly through the remainder of the circuit.

The metal connectors and opaque section of latex tubing in the circuit are jolted to dislodge any bubbles which may have been trapped, and a clamp is applied to the distal end of the arterial line.

(2) Priming with Ringer's Lactate.

Once the dog's heart has been exposed, Ringer's lactate is pumped into the mixing chamber by way of the venous pump. The flow of oxygen is regulated so that the bubbles only just rise in the mixing chamber. The Ringer's lactate-oxygen mixture therefore enters the debubbling can very slowly. The fluid trickles gently into the helix, causing no turbulence and avoiding the formation of bubbles within the helix.

OPERATIVE PROCEDURE.

EXPERIMENTAL ANIMALS.

Unselected adult mongrel dogs, weighing between 35 and 65 lbs., were used. The animals were starved overnight before operation. On the morning of operation the dog was anaesthetised and the operative field prepared by shaving and the application of antiseptic preparations to the skin (Phisohex and Iodine).

PREPARATION OF PROSTHETIC VALVE.

In all experiments the U.C.T. lenticular mitral prostheses Mark IIa and b and Mark III (canine size) were used.

On the morning of the experiment the Dacron cloth suture ring is secured to the steel rim of the prosthesis, which is then autoclaved for 10 minutes.

ANAESTHETIC.

Anaesthesia was induced with a 5% sodium pentothal solution administered intravenously, 10 ml. usually being sufficient. A cuffed endotracheal tube was inserted and anaesthesia maintained by means of nitrous oxide and oxygen. The cuff was blown up and intermittent positive pressure respiration continued until total cardiopulmonary bypass was commenced.

MONITORING.

1. Temperature:

Leads from the Universal electrothermometer were placed in

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the oesophagus and rectum of the experimental animal for the recording of these temperatures.

2. Electrocardiography:

Subcutaneous limb leads were inserted and connected to a Siemen's Cardirex for continuous electrocardiographic monitoring.

3. Arterial and Venous Pressures:

Both groins were prepared with antiseptic applications and draped with sterile towels. The left common femoral artery and vein were dissected free, cannulated with polythene tubing, and connected to the Cardirex for continuous monitoring of the arterial and venous pressures during and after the operation.

EXPOSURE OF THE HEART.

The thoracic cavity was entered through a left thoracotomy at the level of the 4th rib bed. Haemostasis is carefully ensured by coagulation diathermy. The lung was retracted posteriorly and the pericardial sac opened by means of a longitudinal incision, anterior to the left phrenic nerve. A transverse incision in the right flap provides better exposure of the heart.

Left atrial and ventricular pressures were then recorded.

PREPARATION FOR CARDIOPULMONARY BYPASS.

1. Arterial Cannulation.

The animal is heparinised using 1.5 mg. heparin for each kilogram of body weight. The right common femoral artery is exposed and encircled with a cotton tape. An arteriotomy is performed and

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the largest possible diameter metal cannula (either 3.5 or 4.0 mm. internal diamter) is inserted retrograde fashion for about 1 inch. This cannula is secured in place with the cotton tape and is connected to the prepared arterial line of the oxygenator.

2. Venous Cannulation.

The tip of the right atrial appendage is gently lifted with Roberts' forceps and an atrial clamp is placed as close to the base of the atrium as possible. A purse-string suture of '0' silk is placed in the base of the atrial appendage, just below the clamp, and the tip of the appendage is incised. The incision is held open with two arterial forceps and a single No. 30 Bardic venous catheter is inserted into the right atrium. This catheter is secured in place with the purse-string suture and it is connected to the venous line of the oxygenator.

BYPASS TECHNIQUE.

To minimise the homologous blood reaction (Litwak et al, 1963; Gadboys et al, 1962), bypass is commenced with Ringer's lactate solution only and cooling is commenced (Gadboys et al, 1964). The fresh heparinised donor blood (500 ml.) is added after 10 minutes over a period of up to 30 minutes. The animal is routinely perfused at 100 cc./kilogram body weight/per minute throughout the bypass.

A thin silk purse-string suture is inserted in the pulmonary artery and a polythene catheter is passed through this vessel into the right ventricle to drain any blood not removed from the atrium.

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Cooling is discontinued at an oesophageal temperature of about 31°C, and the heart is electrically fibrillated.

EXCISION OF MITRAL VALVE.

The left atrial appendage is opened and the incision extended across the atrial wall to the margin of the inferior pulmonary vein. The atrial margins are grasped with Millin's prostatectomy forceps and pulled upwards. In this way an excellent view of the mitral valve is obtained.

A nerve hook is used to lift the chordae of the anteromedial and posterolateral cusps, and these anchors are divided flush with their papillary muscles. Both anteromedial and posterolateral mitral cusps are then excised.

INSERTION OF THE PROSTHETIC VALVE.

(A) SUPRA-ANNULAR INSERTION. (Figs. 23 a, b, c, d, and e).

Three '0' double-armed black silk mattress sutures are carefully passed from ventricular to atrial sides through the mitral annulus. Twelve of these are usually adequate. Four stay sutures are first passed through the Dacron cloth suture ring, at points directly opposite their insertion in the annulus, with great accuracy (Figs. 23 a and b), to facilitate the correct insertion of the prosthesis (Fig. 23 c). When all the sutures are in place, the prosthesis is guided into the atrium until it fits snugly on the annulus. The sutures are tied and the ends cut flush with the knots (Fig. 23 d).

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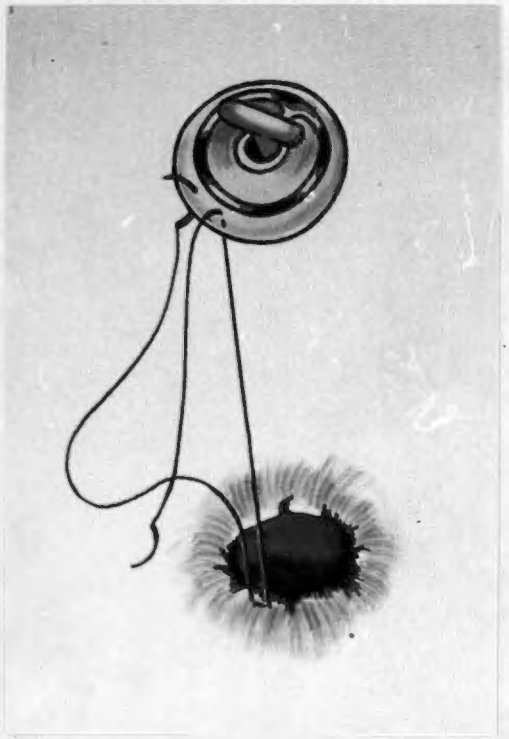

Fig. 23 a

Diagram illustrating the commencement of supra-annular placement of the UDT mitral prosthesis; using interrupted silk mattress sutures passed from ventricular to atrial sides of the mitral annulus.

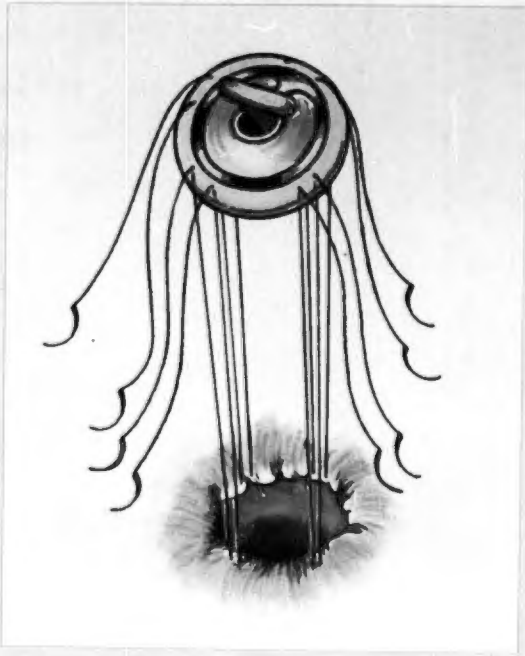

Fig. 23 b.

Supra-annular placement of the UCT prosthesis: the four stay sutures are in position.

On completion of the insertion, part of the Dacron suture ring, the stainless steel frame and the suture knots are all exposed to left atrial blood flow (Fig. 23 e).

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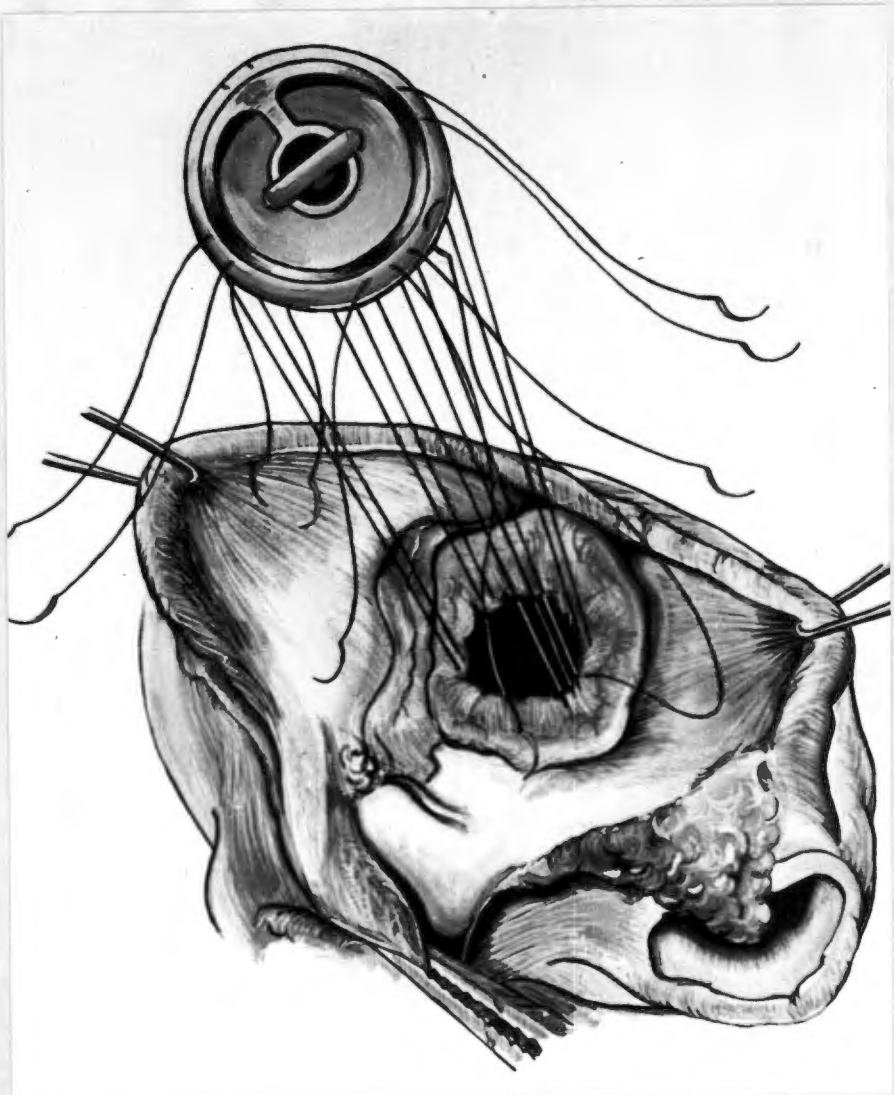
Fig. 23 c.



This drawing illustrates the careful placement of sutures, at points in the suture ring directly opposite their insertion in the mitral annulus, to avoid undue tension.

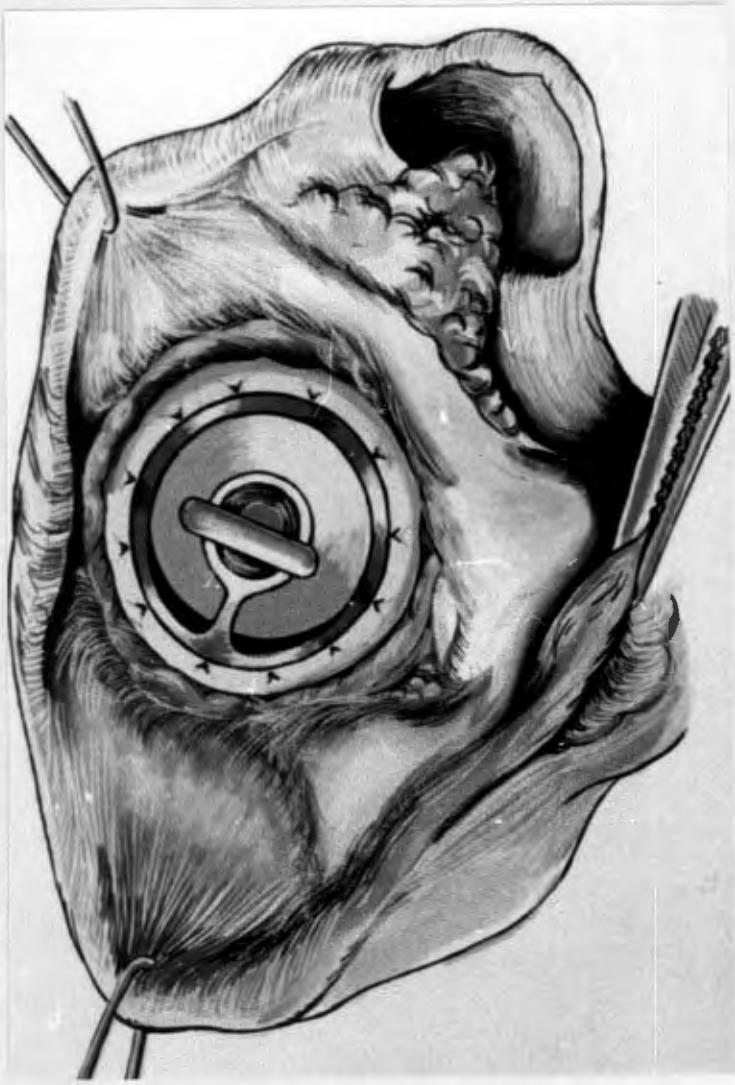


Fig. 23 d.

Supra-annular placement of UCT prosthesis: Drawing showing how, when the valve is in position, a large portion of the Dacron suture ring, the metal framework and the suture knots, are all exposed to the left atrial environment.

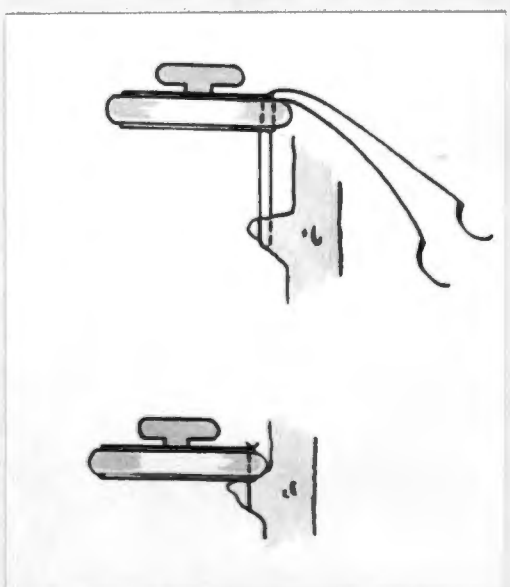


Fig. 23 e

Diagram showing the side view of supra-annular placement of the U.C.T. mitral prosthesis.

(B) SUBANNULAR INSERTION (Figs. 24 a, b, c, d and e).

Although technically more difficult, this method is very similar to that described above. Four silk mattress stay sutures are first passed through the Dacron suture ring of the prosthesis (Fig. 24 a) and are then passed from ventricular to atrial sides through the mitral annulus (Fig. 24 b). The remaining sutures are then carefully inserted (Fig. 24 c). The prosthesis is pushed into the ventricular cavity and the sutures are tightened. The valve is pulled up on the ventricular side of the mitral annulus. The sutures are tied and the ends cut flush with the knots (Fig. 24 d).

Only the suture knots, a small rim of steel and the steel suspension arm are exposed to the left atrial environment. The Dacron cloth suture ring is exposed to the ventricular blood flow, being completely covered by the annulus (Fig. 24 e).

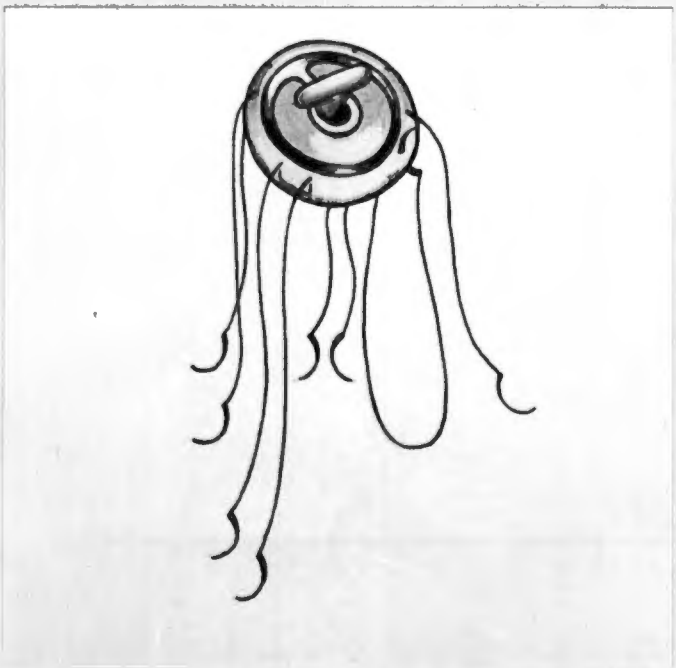


Fig. 24 a.

Subannular Insertion of UCT Mitral Prosthesis: Diagram illustrating the placement of the two 'O' interrupted silk mattress stay sutures through the prosthesis' suture ring.

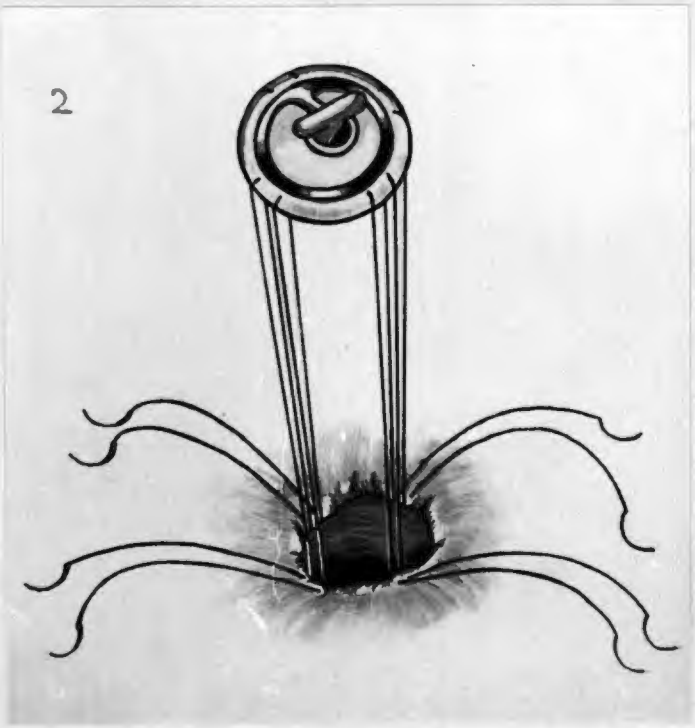


Fig. 24 b.

Subannular insertion of UCT Mitral Prosthesis: The four stay sutures have been inserted, passing through the annulus from the ventricular to the atrial side.

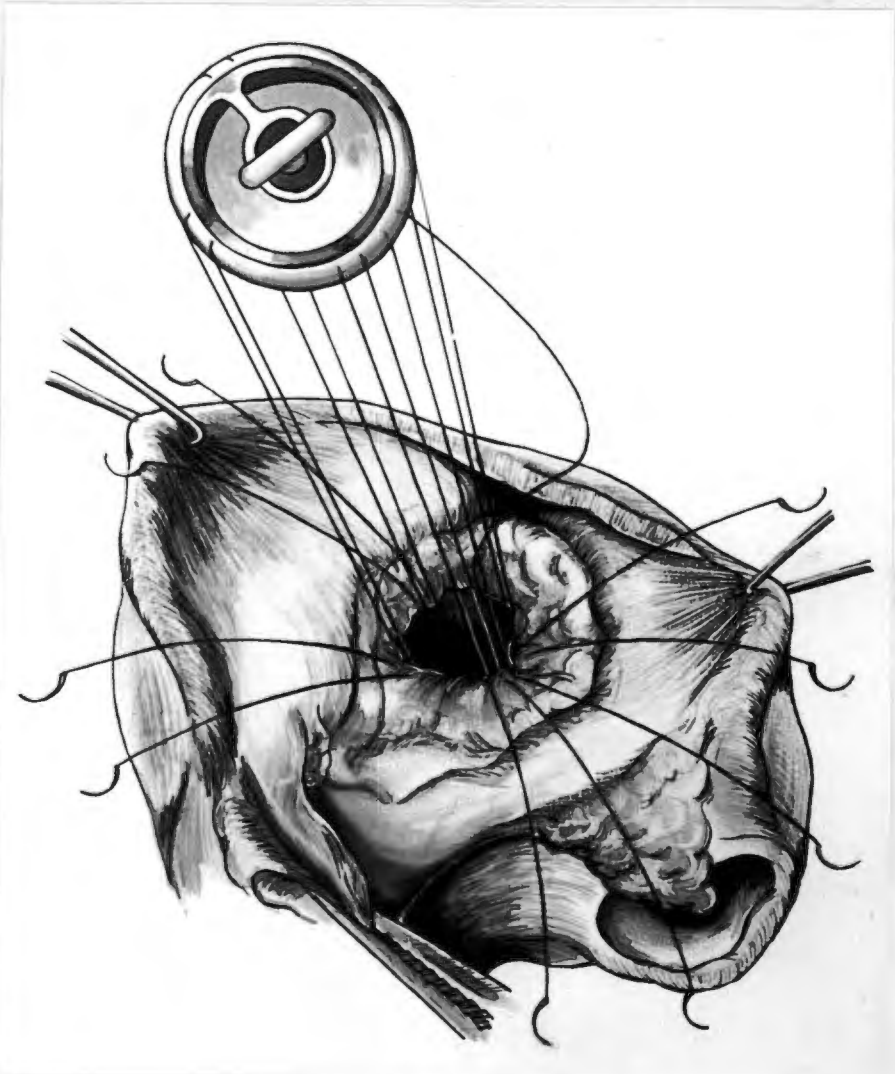


Fig. 24 c.

Drawing showing the careful insertion of the interrupted silk mattress sutures through the Dacron suture ring and then through the annulus directly opposite, to minimise tension.

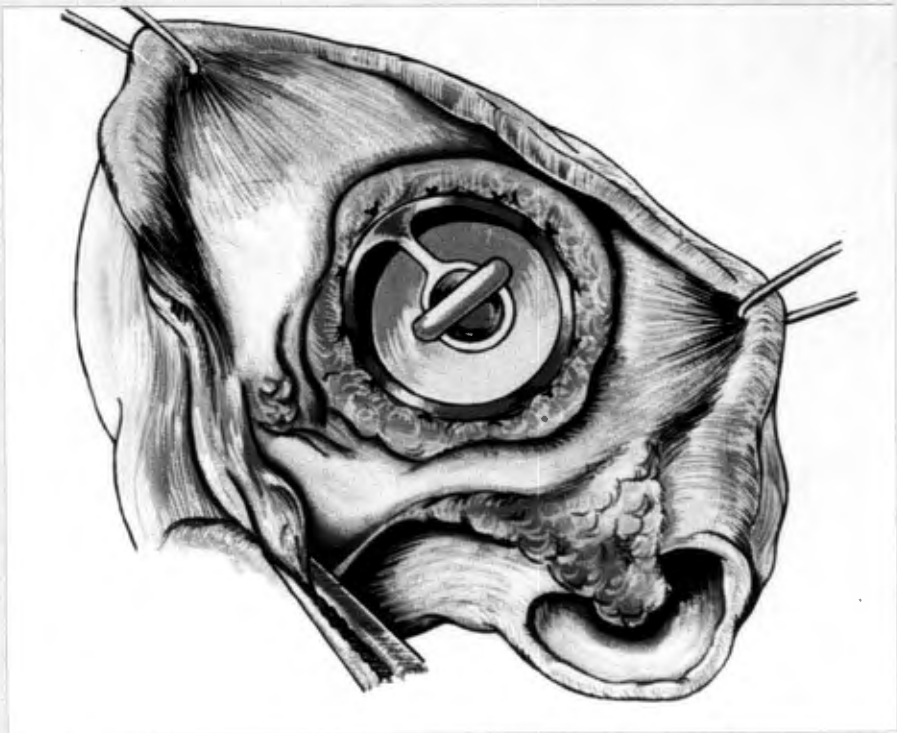
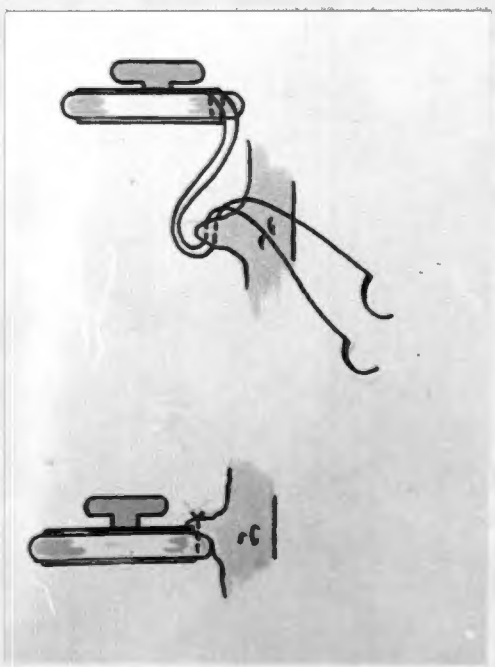


Fig. 24 d. When the prosthesis is in position subannularly, the Dacron suture ring is covered by the fringe of the annular remains.

Fig. 24 e.

Diagram illustrating the side view of the UCT Mitral prosthesis inserted below the annulus.



Once the prosthesis is in place, supra- or subannularly, the area is carefully inspected and probed to detect any areas of incompetence. If present, additional sutures are inserted.

A catheter is placed through the mitral orifice into the left ventricle, to keep the valve incompetent, decompressing the left ventricle and allowing air to escape from the left heart. The left heart is allowed to fill with blood.

CLOSURE OF THE HEART AND DISCONTINUATION OF BYPASS.

The atriotomy is carefully repaired with a single layer of three '0' black silk. The atrial appendage and catheter are loosely tied.

When the oesophageal temperature reaches 36°C, on rewarming, the heart is electrically defibrillated. As soon as its action is satisfactory, the vent in the left ventricle is removed. Bypass is discontinued.

At the stage when rewarming is commenced, arterial blood samples are taken for acid-base studies and serum electrolyte estimation. As soon as these findings are available any deviation from normal is corrected.

At the end of bypass, the dog's blood volume is corrected by perfusing the amount required from the oxygenator, guided by the arterial and venous pressures.

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The heparin is neutralised with protamine (mg. for mg.).

The Bardic catheter is removed from the right atrium and the atrial appendage is doubly ligated with the purse-string suture.

All parts of the operative field are carefully examined to ensure proper haemostasis.

The pressures in the left atrium and left ventricle are recorded.

The right common femoral artery cannula is removed and the opening ligated.

The pericardial sac and left pleural cavity are drained and the chest wall is closed in layers.

POST-OPERATIVE TREATMENT.

All the dogs received antibiotics, intramuscular tetracycline and penicillin, on the day of operation and on the following four days. The chest drain is removed as soon as there is no further blood loss, usually on the evening of the day of operation.

None of the dogs in this study received anticoagulant therapy post-operatively.

The following post-operative treatment was carried out in 5 animals: on the 3rd post-operative day 300,000 ml. of streptokinase* are dissolved in 150 cc. of 5% dextrose in water, and this solution is slowly administered intravenously over 6 to

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* "Streptase" - Behringwerke A.G.

8 hours. This treatment was repeated daily until the 8th post-operative day.

"Streptase" is a highly purified streptokinase preparation derived from culture of B-haemolytic streptococci belonging to Lancefield Group C. Attempts were made to digest thrombus present in the last-mentioned 5 dogs by the intravenous administration of "streptase", after insertion of the prosthetic valve.

CATHETER STUDIES.

APPARATUS.

Haemodynamic data is obtained using two Statham P.23 D.6 strain gauge transducers coupled to Hellige M.A.88 carrier amplifiers, the outputs of which are fed directly into a 6 channel N.E.P. Honeywell photographic recorder. Electrical and hydraulic sine wave and square wave tests proved both transducer-amplifier-recorder chains to behave identically in respect of linearity; damping and frequency response was well above the normal physiological range.

A model K.100A Wates photo tube densitometer and control unit were used for evaluation of dye indicator curves. The electrical output is directly connected to one channel of the galvanometer recorder. Constant withdrawal of dyed blood was performed with a Havard infusion/withdrawal pump.

Cine-angiocardiograms were recorded on a 16 mm. Arriflex camera mounted above a 5 inch Philips intensifier unit. A Talley injection pump was used to infuse contrast media (60% Hypaque) rapidly into the left ventricle for study of competence of the mitral valve.

METHOD.

The animal is anaesthetised with sodium pentothal, oxygen and nitrous oxide, and 5,000 units of heparin are given intravenously. The right external jugular vein and common carotid artery are

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isolated through a longitudinal skin incision. A No. 6 Lehman's catheter is introduced into the right atrium via the external jugular vein. The right ventricle is then entered and a withdrawal tracing obtained back to the right atrium. The catheter is advanced into the main pulmonary artery and withdrawn into the right ventricle. The catheter is then wedged in a distal pulmonary artery. This is repeated at a number of sites, but always on the right side as it was felt that there might have been post-operative lung damage on the left side following thoracotomy. Satisfactory wedge tracings are confirmed by the wave form, and the presence of a good "snap free" into the pulmonary artery on withdrawal.

The Lehman's catheter is left in the wedge position and a No.6 Rodrigues-Alvarez catheter introduced via the right common carotid artery into the left ventricle. With equisensitive manometers, simultaneous tracings are made from the left ventricle and the wedge position. An attempt is made to simulate exercise by amyl nitrite inhalation, and these tracings are repeated.

The venous catheter is then withdrawn and, with the dog in the right anterior oblique position, cine-angiocardiography is performed (Fig. 38) to demonstrate the degree of competence of the mitral prosthesis and to assess left ventricular function.

The Rodrigues-Alvarez catheter is withdrawn into the aorta and the Lehman's catheter re-introduced into the pulmonary artery. Quantitative indicator dye studies areperformed, both before and after amyl nitrite inhalation. One ml. indocyanine (1.25 mg. per ml.) is injected into the main pulmonary artery and arterial blood

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sampled through the densitometer. Quantitative estimation of cardiac output is performed by the dye dilution method of Hamilton et al (1948).

Sterile technique is used throughout. When satisfactory dye curves have been obtained, the catheters are withdrawn, the artery and vein are ligated, and the skin is sutured. Antibiotic cover with penicillin and tetracycline is provided pre-operatively, on the day of catheterisation and on the two following days.

RESULTS.

R E S U L T S.

GROUP A - SUPRA-ANNULAR INSERTION OF THE MITRAL PROSTHESIS.

The U.C.T. mitral prosthesis was placed in the supra-annular position in 16 dogs. Of these, 6 died within 24 hours. None of the remaining 10 animals survived longer than 8 days.

DOGS SURVIVING LESS THAN 24 HOURS (Table 1).

These animals died as a result of technical failure and/or inadequate perfusion.

Table 1.

DOG	PROSTHESIS	SURVIVAL	CAUSE OF DEATH.
1	Mark IIa	1 hour	Ventricular fibrillation. Metabolic acidosis.
2	Mark IIa	6 hours	Faulty suture of prosthesis. Gross mitral incompetence.
3	Mark IIb	30 mins.	Ventricular fibrillation. Metabolic acidosis.
4	Mark IIa	16 hours	Faulty suture of prosthesis. Gross mitral incompetence.
5	Mark IIb	6 hours	do.
6	Mark IIb	15 mins.	Ventricular fibrillation. Metabolic acidosis.

DOGS SURVIVING LONGER THAN 24 HOURS (Table 2).

One dog died 36 hours after operation and never regained consciousness; air embolism was the cause of death. Careful

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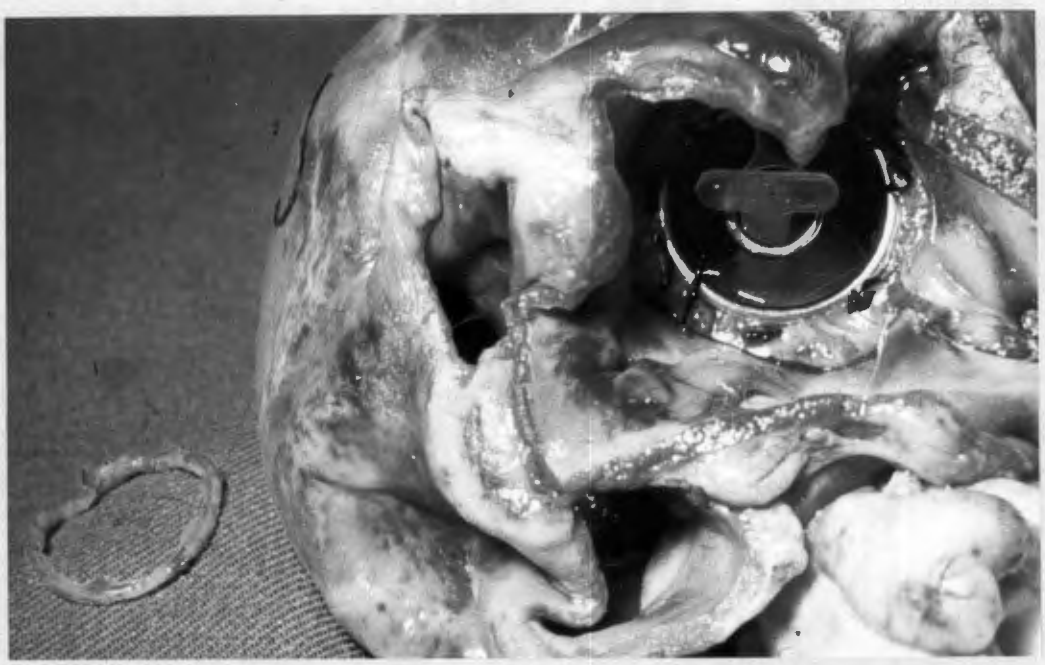
examination of the heart post mortem showed that a fibrin thrombus had formed at the junction of the Dacron suture ring with the annulus, even at this early stage (Fig. 25 a). No thrombus was visible on the ventricular side of the annulus (Fig. 25 b).

Fig. 25 a.



Supra-annular insertion of the UCT mitral prosthesis: post mortem specimen in a dog which died 36 hours after operation from air embolism. Fibrin thrombus had already begun to form at the junction of the Dacron suture ring with the annulus. The thrombus ring has been removed and is to be seen in the lower left corner of the photograph.

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Fig. 25 b.

Post mortem specimen in the same dog as Fig. 25 a. The ventricular side of the mitral annulus and prosthesis, quite free of thrombus.

The remaining 9 survivors all presented very similar clinical courses after surgery and died within 8 days. Necropsy revealed similar findings in each.

Clinical Course:

During the first two post-operative days the dogs appeared well. There was no dyspnoea and all animals could stand and walk short distances. Urinary output was satisfactory.

From the 3rd or 4th post-operative day, shortness of breath became apparent and some oedema of the hindlegs appeared. From

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this time there was rapid deterioration with increasing dyspnoea, refusal of food and increasing oedema of the legs. The majority of animals also experienced haemoptysis. When it became clear that these animals could not survive they were heparinised and sacrificed, using 10 cc. of sodium pentothal given intravenously.

Necropsy Findings:

There was no sign of wound sepsis in any of the dogs and healing of the incision appeared to be progressing normally.

Lungs: Some fibrinous exudate was present on the pleura. Large amounts of pleural exudate were present. The lungs were oedematous and, on section, copious amounts of frothy, blood-stained fluid oozed from the cut surfaces.

Liver: Normal.

Kidneys: These appeared normal without evidence of any infarction.

Heart: The left atrial cavity was invariably filled with a large fibrin thrombus. In all the dogs this had originated at the junction of the annulus with the Dacron suture ring, and at any area of trauma on the atrial wall. From here it had spread into the atrial cavity and over the prosthesis until it occluded the valve orifice (Fig. 26 a, b and c). A most striking finding in all these hearts was the absence of significant thrombus on the ventricular side of the annulus or prosthesis (Fig. 26 d). The thrombus that could be seen on the ventricular side had originated in the atrium, spread over the prosthesis and extended down

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the orifice into the left ventricle (Fig. 26 e).

On examination of the aorta and the large vessels, no thrombus was found.

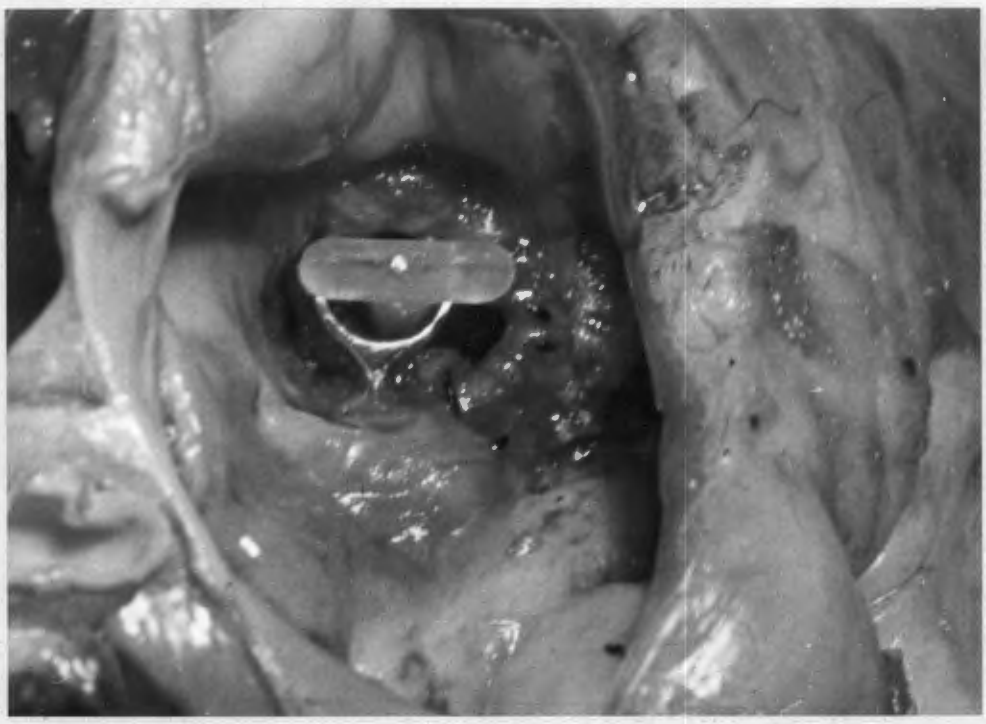

Fig. 26 a.

Supra-annular insertion of the UCT mitral prosthesis: Post mortem specimen in a dog dying 5 days post-operatively. The valve orifice seen from the left atrial side is almost occluded by a fresh thrombus which extends well up into the atrium.

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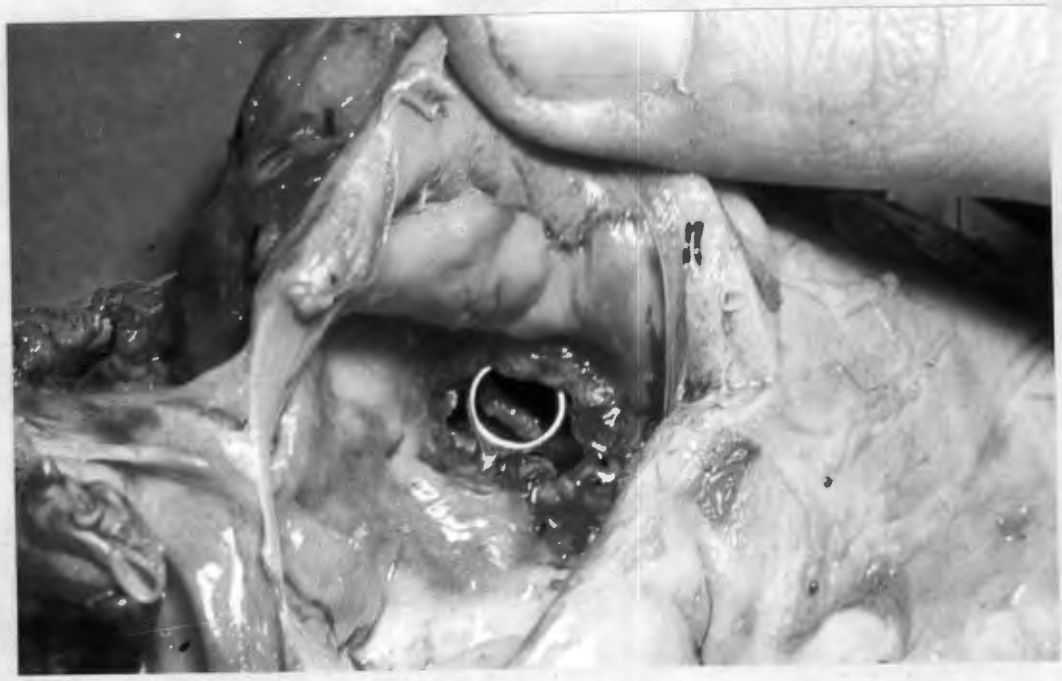
Fig. 26 b. The same post mortem specimen after removal of the ball from the prosthesis.



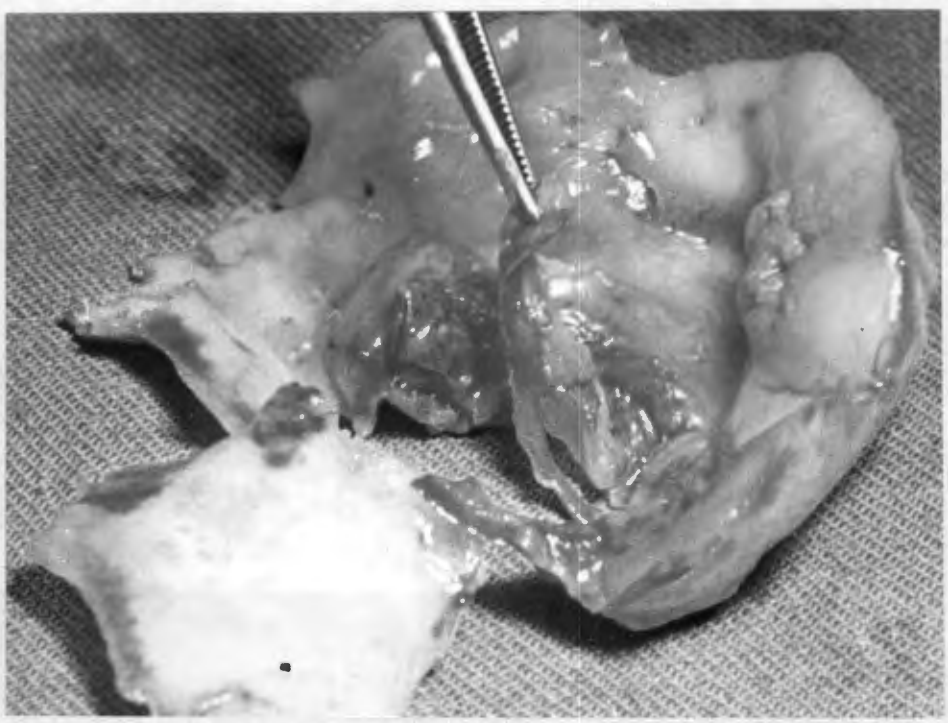
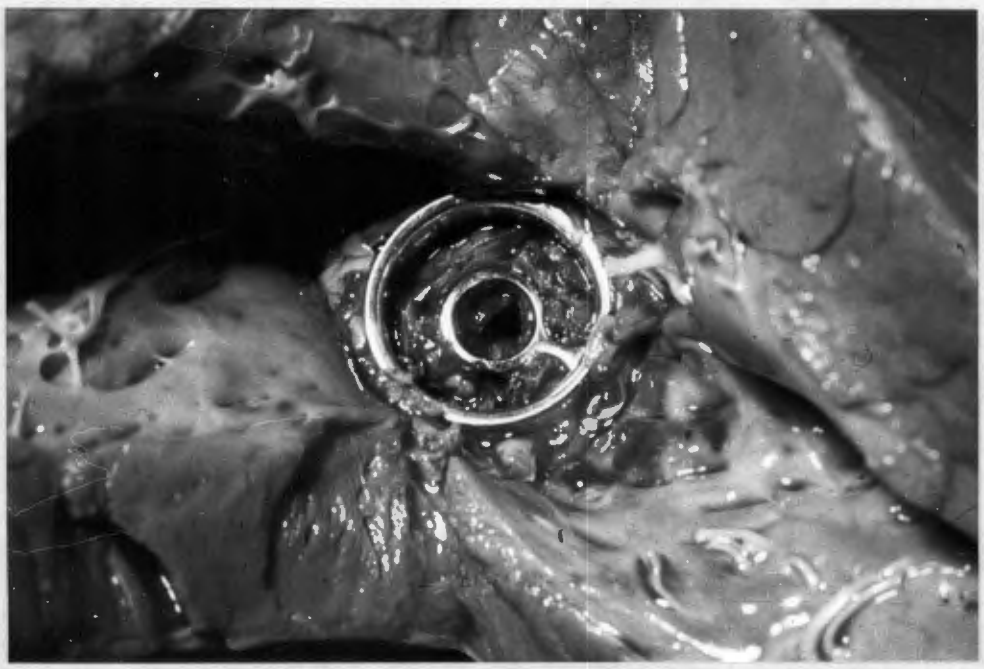


Fig. 26 c. The same post mortem specimen. This photograph shows the extent of the atrial thrombus after removal of the thrombus from the prosthesis and left atrial wall.

Fig. 26 d.



The same specimen post mortem. This photograph shows the ventricular side of the prosthesis and annulus. The thrombus from the atrial side has almost completed obstructed the orifice. There is minimal thrombus on the prosthesis.

Fig. 26 e.

The same post mortem specimen. Photograph showing the thrombus originating in the left atrium extending through the mitral orifice into the left ventricle.

Table 2.

DOG	PROSTHESIS	L.A. PRESSURES* Pre-Bypass	Post-Bypass	SURVIVAL	COURSE.
7	Mark IIb	12/8	35/20	5 days	Died. Gross pulmonary oedema. Thrombus occluding valve.
8	Mark IIb	12/6	16/8	1½ days	Died. Minimal atrial thrombus Air embolism.
9	Mark IIa	16/4	17/5	8 days	Died. Gross pulmonary oedema. Thrombus occluding valve.
10	Mark IIa	14/8	16/4	5 days	do.
11	Mark IIb	8/4	30/15	5 days	do.
12	Mark IIa	12/6	16/10	5 days	do.
13	Mark IIa	14/8	20/6	6 days	do.
14	Mark IIb	4/0	8/4	5 days	do.
15	Mark II b	12/6	19/10	5 days	do.
16	Mark IIb	14/8	18/12	6 days	do.

* mm.mercury.

It was concluded that the insertion of the U.C.T. mitral prosthesis in the left atrium of a dog's normal heart results in thrombosis in the left atrium, occlusion of the valve orifice and death within 8 days.

GROUP B. SUBANNULAR INSERTION OF THE MITRAL PROSTHESIS.

The U.C.T. mitral prosthesis was placed in the subannular position in 17 dogs. Of these, 6 died within 24 hours. Of the 11 survivors, 5 dogs died within 12 days and the remaining 6 survived more than one month. Four dogs are still alive and well, between four and six months following operation.

DOGS SURVIVING LESS THAN 24 HOURS (Table 3).

These animals died as a result of technical failure and/or inadequate perfusion.

Table 3.

DOG	PROSTHESIS	SURVIVAL	CAUSE OF DEATH.
1	Mark IIa	16 hours	Faulty suture of valve. Gross mitral incompetence.
2	Mark III	6 hours	do.
3	Mark IIb	30 mins.	Ventricular fibrillation. Metabolic acidosis.
4	Mark IIb	12 hours	Faulty suturing of valve. Gross mitral incompetence.
5	Mark III	6 hours	do.
6	Mark III	4 hours	do.

DOGS SURVIVING FROM 1 TO 12 DAYS (Table 4).

One animal in this group died after 36 hours, as a result of air embolism. In contrast to the dog in Group A which died after 36 hours, there was no thrombus on the atrial surface of the

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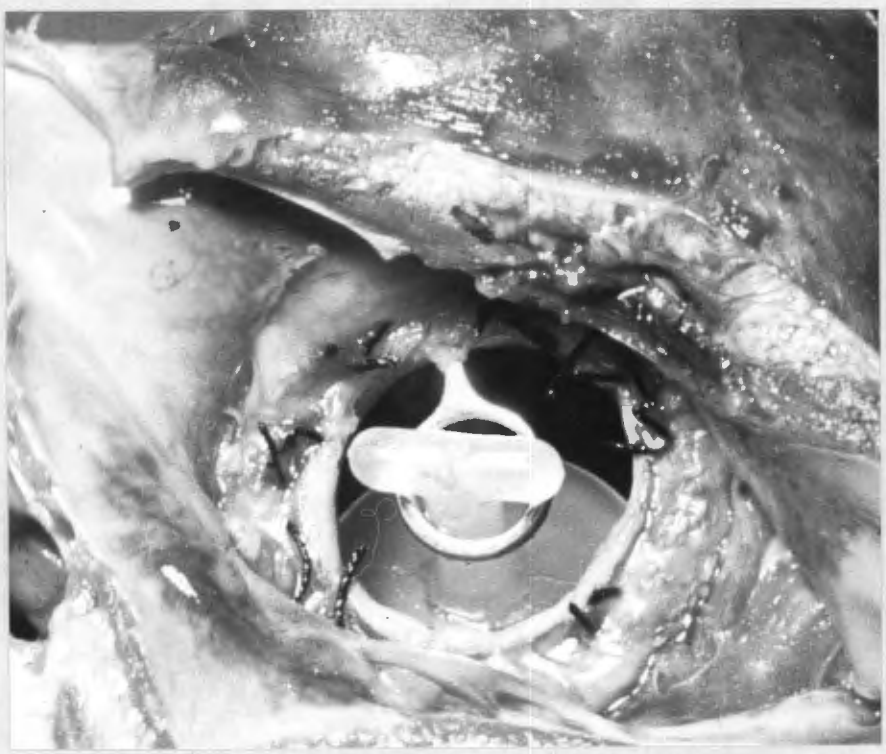
prosthesis at post mortem (Fig. 27 a). The Dacron cloth suture ring, exposed to the ventricular environment, showed no evidence of fibrin deposition (Fig. 27 b).

Fig. 27 a.



Subannular Insertion of UCT Mitral Prosthesis. Post mortem specimen in the dog which died 36 hours after surgery, from air embolism. Note the absence of fibrin thrombus on the left atrial side of the mitral annulus.

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Fig. 27 b.

Subannular Insertion of U.C.T. Mitral Prosthesis. Post mortem specimen of same dog (Fig. 27 a) showing the ventricular side of the annulus. The Dacron suture ring and steel rim of the prosthesis show no evidence of fibrin thrombus.

Clinical Course:

The other 4 animals in this group appeared to recover well from the operation. However, on the 3rd - 5th post-operative day these dogs became dyspnoeic and oedema of the hindlegs became apparent. Increasing dyspnoea, haemoptyses and increasing oedema progressed rapidly. When the fatal termination of these dogs' course became inevitable, they were heparinised and sacrificed.

Necropsy Findings:

There was no evidence of wound sepsis and the healing of the incision was satisfactory.

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Lungs: The pleural cavity was filled with fluid and the lungs were oedematous. On section of the lungs, copious amounts of frothy, blood-stained fluid oozed from the cut surfaces.

Liver: Normal.

Kidneys: Normal in appearance and there was no evidence of infarction.

Heart: The left atrial cavity was filled with a large fibrin thrombus. In two specimens, faulty suturing of the prosthesis (or disruption of sutures) resulted in mitral incompetence and the thrombus appeared to originate at the site of the incompetent jet, (Fig. 28a). In the other two specimens, the thrombus originated from the annulus and areas of trauma to the left atrial wall. In all 4 hearts the Dacron cloth suture ring and the ventricular aspect of the prosthesis was free of thrombus (Fig. 28 b).

There was no evidence of thrombi in the aorta or the great vessels.

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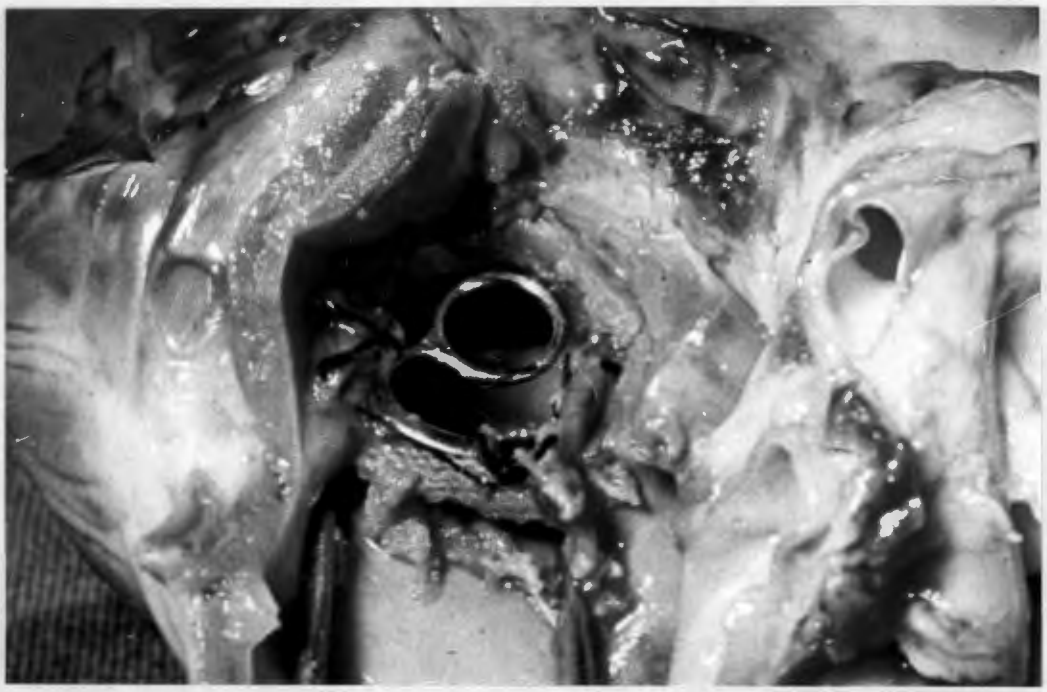
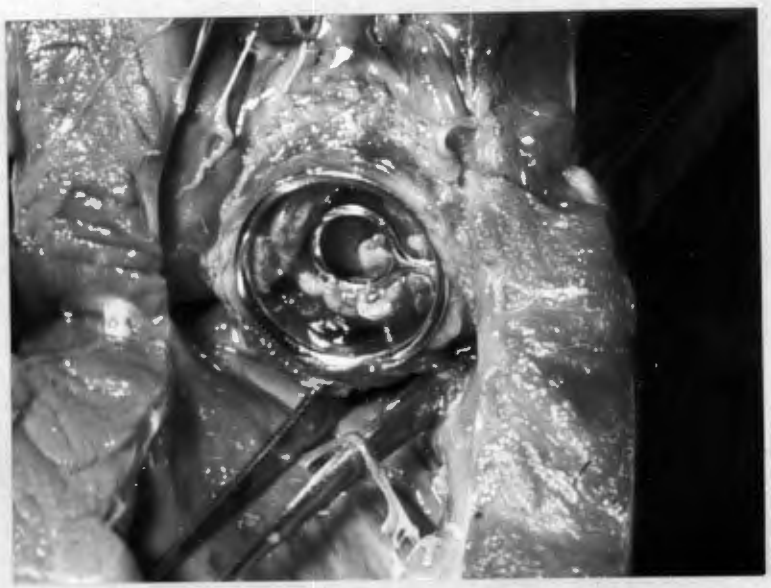
Fig. 28 a.



Subannular Insertion of UCT Mitral Prosthesis: Post mortem specimen of dog which died 8 days post-operatively from gross mitral incompetence, due to faulty suture of the prosthesis. The photograph shows the atrial aspect - note the disruption of the prosthesis, where maximal thrombus was present, apparently originating at the site of the incompetent jet.

Fig. 28 b.



The ventricular aspect of the same post mortem specimen showing the area of prosthesis disruption. Note the absence of thrombus on the suture ring and metal rim.

Table 4.

DOG	PROSTHESIS	L.A.PRESSURES(mm.Hg) Pre-bypass	Post-bypass	SURVIVAL	COURSE.
7	Mark IIa	10/8	10/8	36 hours	Died. Air embolism. No thrombus.
8	Mark IIb	14/6	30/15	8 days	Died. Pulmonary oedema. Thrombus occluding valve.
9	Mark III	18/10	30/16	8 days	Died. Pulmonary oedema. Mitral incompetence due faulty suture/ disruption of suture.
10	Mark IIb	12/8	35/16	8 days	Died. Pulmonary oedema. Thrombus occluding valve.
11	Mark III	4/0	35/20	12 days	Died. Pulmonary oedema. Thrombus occluding valve. Mitral incomp. due disruption of sutur

DOGS SURVIVING MORE THAN 1 MONTH (Table 5).

Seven animals survived more than a month after subannular insertion of the U.C.T. mitral prosthesis.

Clinical Course:

The dogs all recovered rapidly following operation. There was no evidence of dyspnoea or oedema. After a week, the dog was able to run short distances without becoming dyspnoeic.

Two of these animals have now succumbed.

One dog was sacrificed on the 31st post-operative day, following cardiac catheterisation:-

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Post mortem findings in dog sacrificed on the 31st day post-operatively:

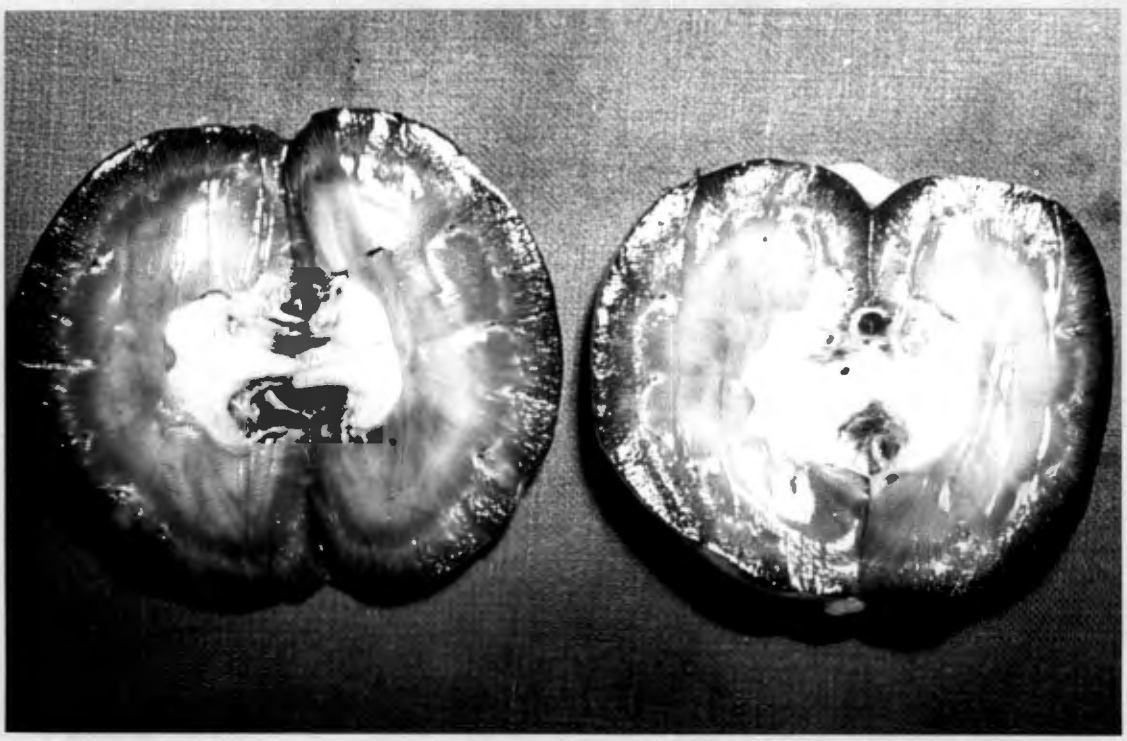
No sepsis was present. Wound healing was normal.

Lungs: The pleural cavity was free of fluid and the lungs were normal except for some adhesions.

Liver: Normal.

Kidneys: Normal and free from infarcts (Fig. 29 a).

Fig. 29 a.



Post mortem specimen of kidney in dog which was sacrificed on the 31st post-operative day after subannular insertion of UCT Mitral Prosthesis. There is no evidence of infarction.

Heart: The left atrium contained a well-organised thrombus arising from the posterior wall and extending into (but not occluding) the valve orifice. This thrombus appeared to

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originate at an area of trauma (Fig. 29 b). On the ventricular side, the Dacron suture ring was covered with healthy, shiny endothelium (Fig. 29 c and d). Adequate invasion of the Dacron cloth by the surrounding tissue was evident. The aorta and large vessels were free of emboli.

Fig. 29 b.

Subannular Insertion of UCT Mitral Prosthesis. Photograph of the atrial aspect in the post mortem specimen of the same dog. Note the absence of thrombus on the prosthesis. There is well organised thrombus arising from the posterior wall (apparently originating at an area of trauma) and extending into the orifice area.

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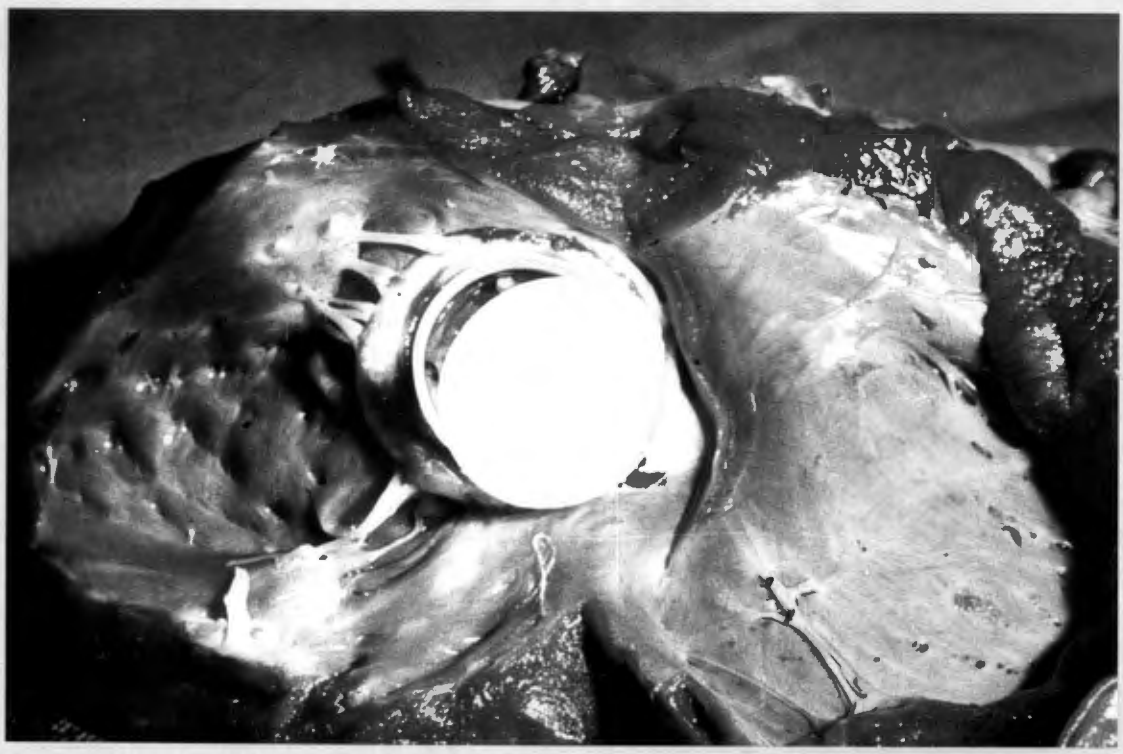
Fig. 29 c.



Post mortem specimen in the same dog after subannular insertion of UCT mitral prosthesis. Photograph shows the ventricular side of the prosthesis and annulus: the Dacron suture ring is covered with healthy endothelium and no thrombus is present.

Fig. 29 d.

Post mortem specimen in the same dog after subannular insertion of UCT mitral prosthesis. Photograph shows the ventricular aspect after removal of the ball from the prosthesis. The Dacron suture ring is covered with healthy endothelium. Thrombus extends from the atrium into the valve orifice. It can be seen clearly that the UCT prosthesis in the subannular position does not obstruct the left ventricular outflow tract.

The second of these dogs which succumbed deteriorated after one month, losing weight and refusing food. It died on the 40th day following surgery.

Post mortem findings in this dog:

There was no evidence of sepsis and the wound was well healed.

Lungs: The pleural cavity was free of fluid and the lungs were normal except for some adhesions.

Liver: Normal.

Kidneys: Bilateral severe chronic renal disease was present with evidence of degeneration of the cortex and numerous cysts were present. No evidence of infarction could be demonstrated. (Fig. 30 a).

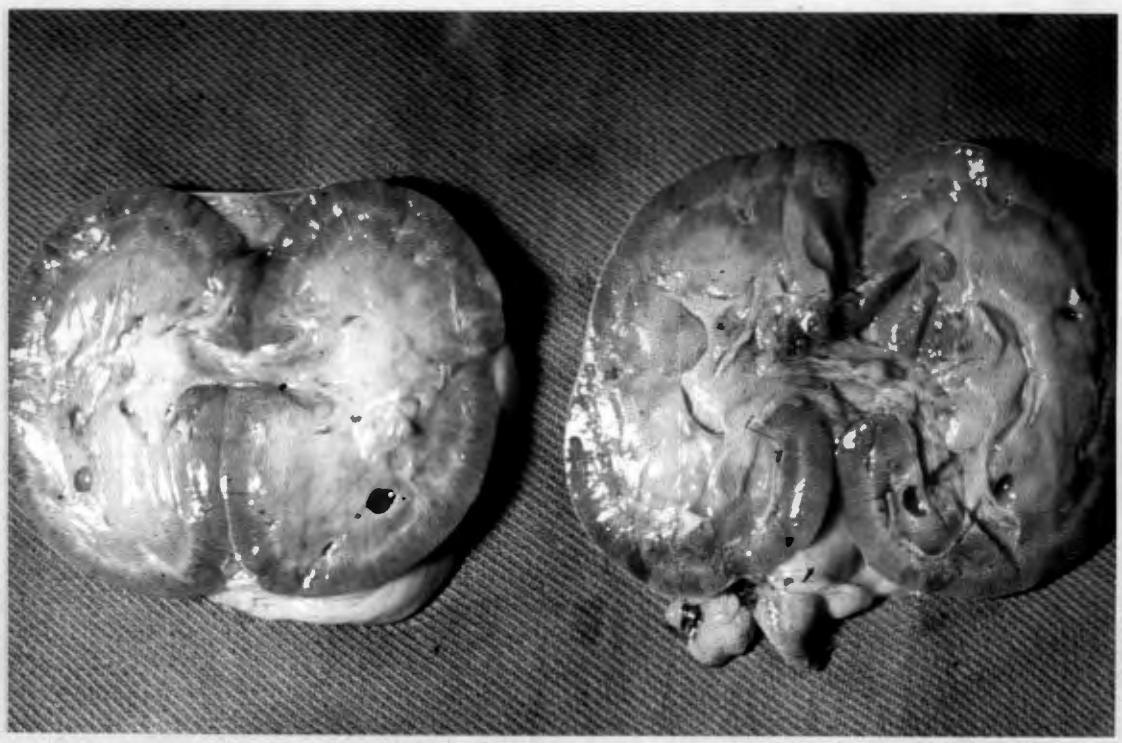


Fig. 30 a. Photograph of post mortem specimen of kidneys in the dog which died 41 days after subannular insertion of the UCT prosthesis. Note the degeneration of the cortex and the multiple cysts. No infarcts are present.

Heart: Minimal organised thrombus was present in the left atrium. The Dacron cloth in the ventricle was covered with normal, shiny endothelium. Adequate invasion of the cloth by the surrounding tissue was evident. The left ventricle was hypertrophied and the left ventricular cavity was significantly smaller than normal (Fig. 30 b).

Fig. 30 b. Photograph of post mortem specimen in same dog from the ventricular aspect, showing the abnormally small ventricular cavity and hypertrophy of the ventricular wall. The Dacron suture ring has been invaded by surrounding tissue and is covered by healthy endothelium.

The left ventricular abnormality found at post mortem confirmed previous cine-angiocardiographic findings. The aorta and large vessels were free of emboli.

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Table 5.

DOG	PROSTHESIS	L.A.PRESSURE (mm.Hg) Pre-bypass	Post-bypass	SURVIVAL	COURSE
12	Mark III	12/6	12/6	5 months	Fit and well.
13	Mark IIb	12/8	16/8	40 days	Died. Small organised atrial thrombus. Abnormal LV. Chronic renal disease.
14	Mark IIb	12/8	19/4	31 days	Sacrificed. Organised atrial thrombus which extended into valve orifice.
15	Mark II b	12/8	14/8	6 months	Fit and well.
16	Mark III	12/6	18/12	4½ months	Fit and well.
17	Mark III	12/6	14/8	4 months	Fit and well.

The remaining 4 survivors in this group are still alive and thriving, between 4 and 6 months after insertion of the prosthesis in the subannular position. Strenuous exercise (a fast run for 400 yards) is eagerly anticipated and is not associated with any more panting than in a normal dog. Weight gain is apparent and there is no clinical evidence to suggest any abnormality.

GROUP C. SUPRA-ANNULAR INSERTION OF MITRAL PROSTHESIS WITH POST-OPERATIVE INTRAVENOUS STREPTOKINASE.

Six dogs constituted this group (Table 6). One animal died within 1 hour of operation, due to ventricular fibrillation. Three dogs survived 12 days following operation and the 2 longest survivors both died on the 31st day after surgery.

DOGS SURVIVING FOR 1 TO 12 DAYS (3 animals).

Clinical Course:

For the first 2 days following operation these dogs recovered normally. On the 3rd day, however, dyspnoea was present. At this stage the intravenous administration of streptokinase was begun. The dyspnoea did not progress while the treatment lasted, but, after cessation of treatment the dyspnoea rapidly became worse and led to death on the 12th post-operative day.

Post Mortem Findings:

No sepsis was present but wound healing was very poor.

Lungs: The pleural cavity was filled with effusion. The lungs were oedematous and, on section, a frothy, blood-stained fluid oozed from the cut surfaces.

Liver: Normal.

Kidneys: Free from infarcts.

Heart: The prosthesis, suture ring and valve orifice were covered with a large, whitish coloured, friable thrombus. The atrial wall was free of thrombus (Fig. 31 a). On the

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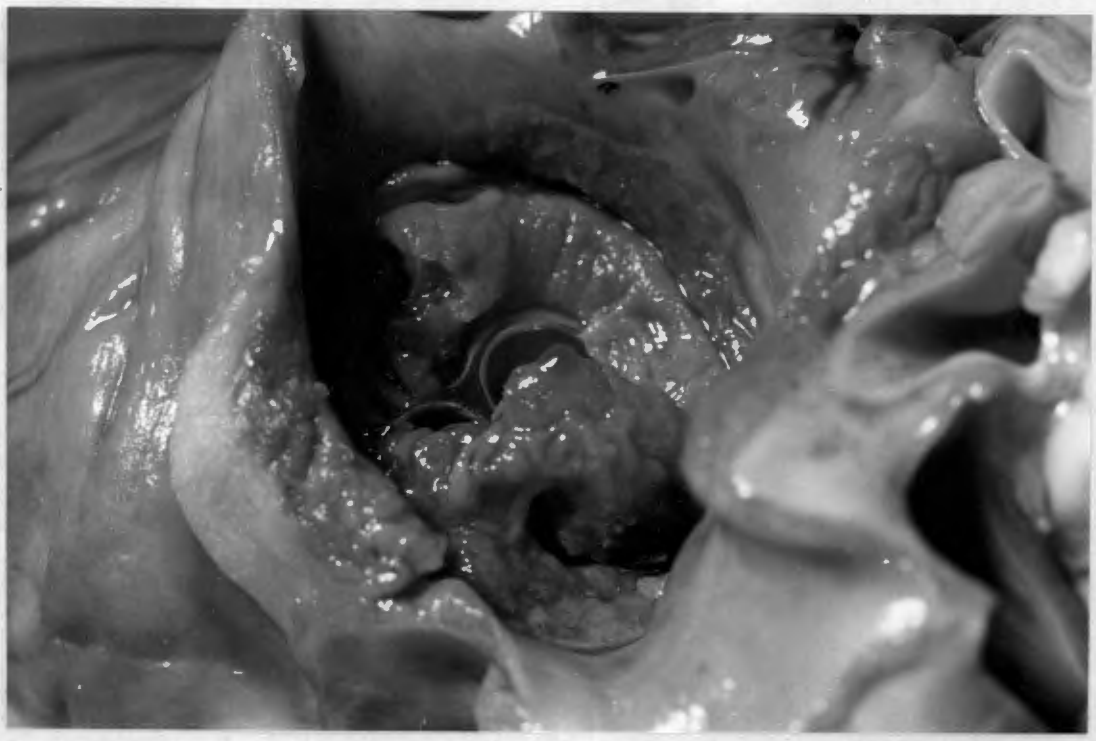
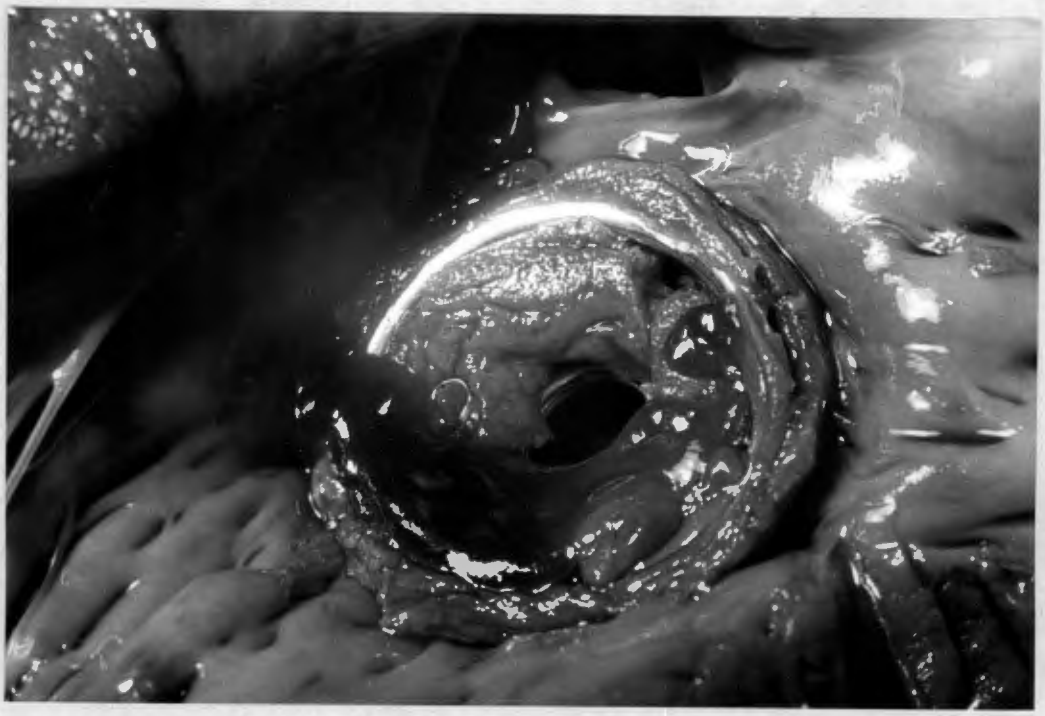
ventricular aspect there was no thrombus on either the prosthesis or the annulus (Fig. 31 b). The aorta and large vessels were free of emboli.

Fig. 31 a.



Post mortem specimen of heart after supra-annular insertion of UCT mitral prosthesis followed by a 5 day course of streptokinase. This dog died 12 days after operation. The photograph shows the atrial view of the mitral area: note the friable, white thrombus which almost completely obstructs the valve orifice.

Fig. 31 b.



Post mortem specimen in the same dog. This photograph shows the ventricular aspect of the mitral area: note the thrombus originating from the atrial side, extending into the valve and occluding the orifice almost completely.

DOGS SURVIVING FOR FROM 12 TO 31 DAYS (2 animals).

Clinical Course:

These dogs recovered reasonably well from the operation but at no time did they thrive. Dyspnoea decreased following the course of streptokinase. From the 21st post-operative day these animals appeared less active and presented with haematuria. Both dogs died on the 31st post-operative day following massive haematuria.

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Post Mortem Findings:

No sepsis was present but the wound healing was grossly delayed. All layers of the incisions fell apart after removal of the sutures.

Lungs: The pleural cavities contained small effusions and the lungs were slightly oedematous.

Liver: Normal.

Kidneys: Multiple infarcts were present on the cut section (Fig. 32 a) and also on the surface of the organs.

Spleen: Multiple infarcts were present (Fig. 32 b).

Heart: The left atrial wall was free of thrombus but the prosthesis and Dacron suture ring were covered with friable, white thrombus (Fig. 32 c). In one specimen, two sutures had disrupted causing dislodgment of the prosthesis (Fig. 32 d). There was minimal evidence of invasion of the Dacron suture ring by annular tissue. The ventricular aspect was free of thrombus. The aorta and large vessels were examined and the presence of emboli confirmed.

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Table 6.

DOG	PROSTHESIS	L.A. PRESSURES(mm.Hg) Pre-bypass	Post-bypass	SURVIVAL	COURSE
1	Mark IIa	11/0	12/8	1 hour	Died. Ventricular fibrillation.
2	Mark IIb	12/6	25/15	31 days	Died. Haematuria. Massive renal emboli. Thrombus on prosthesis. Disruption of prosthesis.
3	Mark IIb	11/6	12/2	31 days	Died. Haematuria. Massive renal emboli. Thrombus on prosthesis.
4	Mark IIb	12/8	19/12	12 days	Died. Gross pulmonary oedema. Thrombus occluding valve orifice.
5	Mark IIa	8/2	8/4	12 days	do.
6	Mark IIa	16/4	17/5	12 days	do.

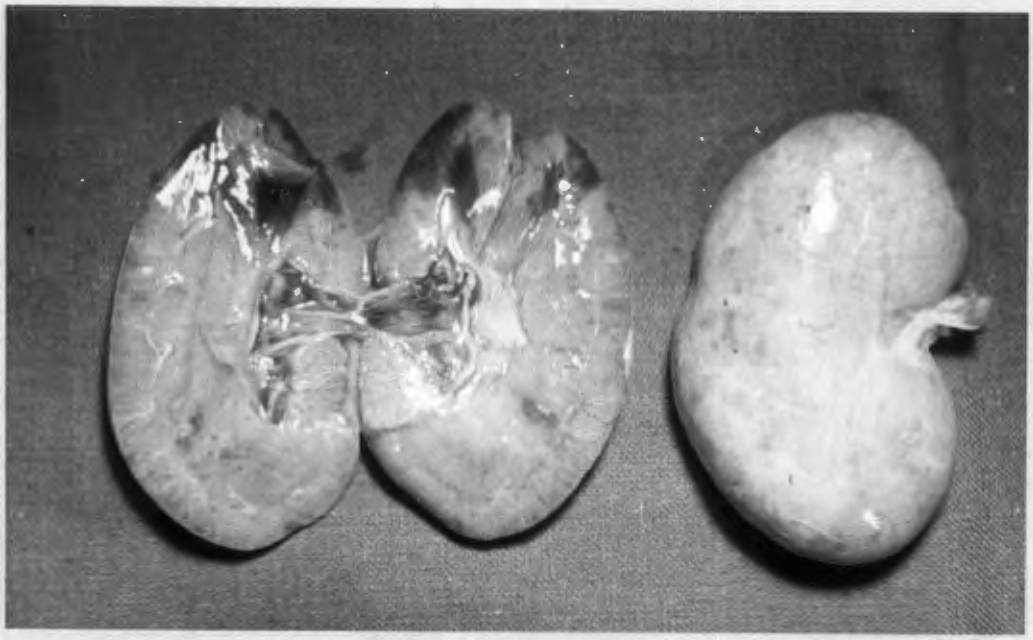


Fig. 32 a

Post mortem specimen of kidneys in a dog which died 31 days after supraannular insertion of UCT mitral prosthesis and a 5 day course of streptokinase. Numerous infarcts are clearly visible.

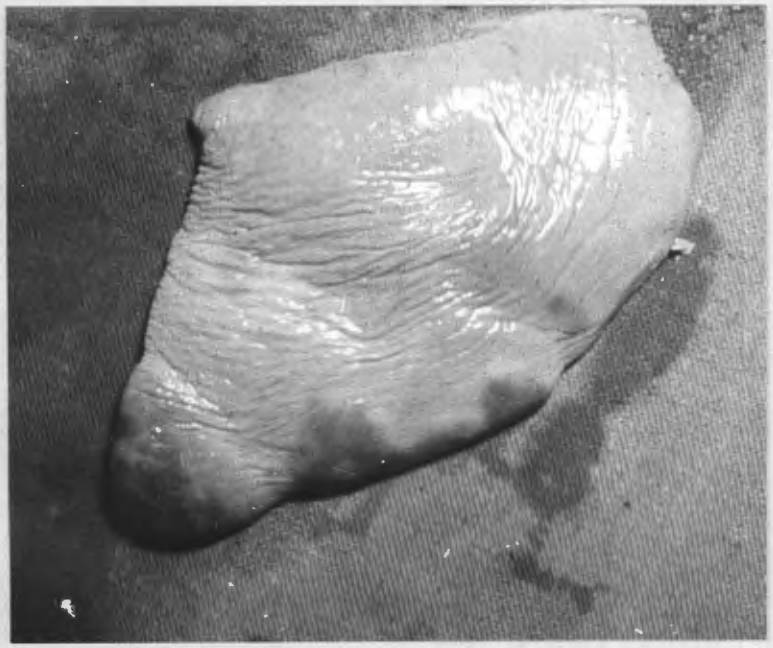


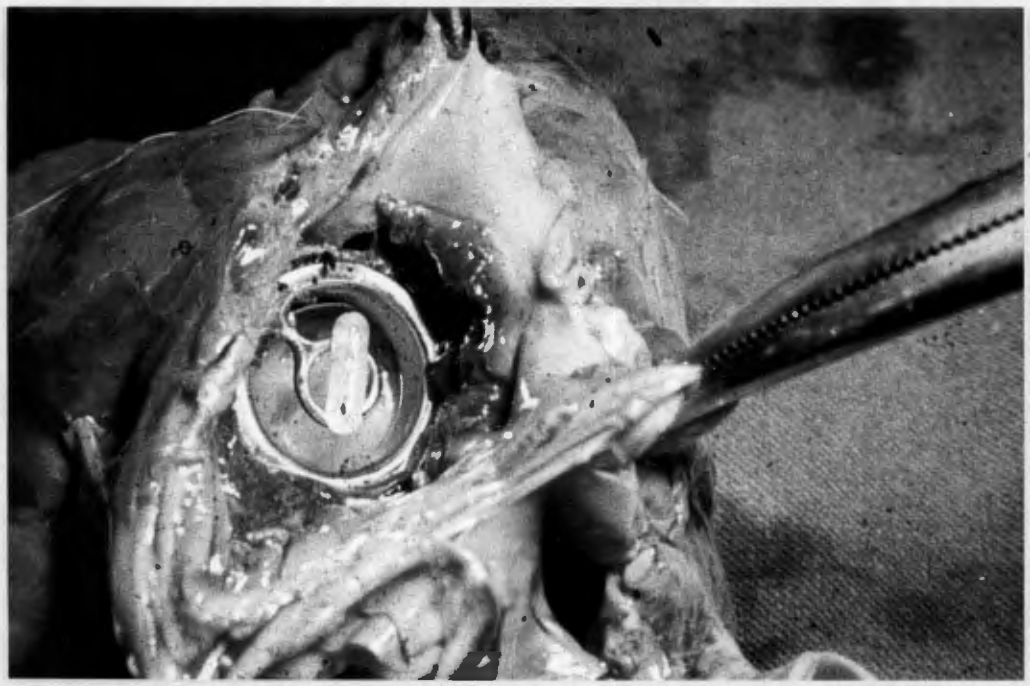
Fig. 32 b.

Post mortem specimen of the spleen of the same dog (Fig. 32 a). Multiple infarcts may be seen.

Fig. 32 c.

Post mortem specimen of the heart in the same dog, the photograph showing the atrial aspect. Friable, white thrombus on the atrial wall extends into the valve but there is no thrombus on the prosthetic suture ring.

Fig. 32 d.



Post mortem specimen of the heart in a dog which died 31 days following supra-annular insertion of the UCT mitral prosthesis, with a 5 day course of streptokinase. The photograph shows the left atrial aspect of the mitral area. Note the disruption of sutures which resulted in mitral incompetence.

HISTOLOGY.

HISTOLOGY.

GROUPS A, B AND C.

LUNGS.

In all the dogs which died as a result of thrombus obstructing the valve orifice, histology confirmed the presence of capillary congestion with haemorrhage into the alveoli.

LIVER.

In all cases, histology of the liver was normal.

KIDNEYS.

Silicone emboli were found in all kidneys examined. Histology of kidneys in dogs with clinical and macroscopic evidence of emboli confirmed the presence of infarcts.

HEART.

(a) Endothelium:

The hearts of the dogs surviving for 1 month or longer showed good invasion of the Dacron cloth by fibrous tissue. Fibroblasts were orientated parallel to the surface of the ventricle, and the outer layer consisted of cells indistinguishable from normal endothelium (Fig. 33).

(b) Annulus:

The most striking histological feature was the constant presence of foci of necrosis of the myocardium at the operative site. In cases where death occurred before 10 days post-operatively, only degenerative changes of the myocardium were detected, but in

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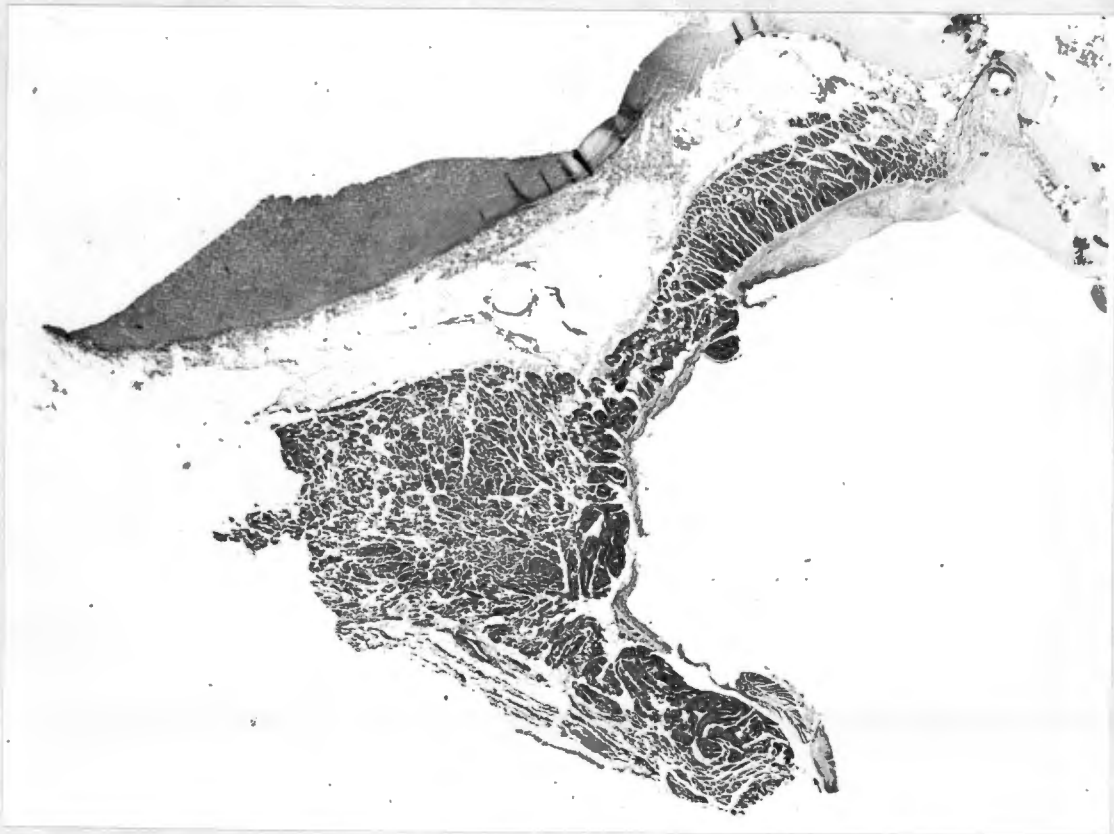
Fig. 33.



Histology of annulus in the dog which was sacrificed 31 days after subannular insertion of the UCT mitral prosthesis. Fibroblasts are orientated parallel to the surface of the ventricle and the outer layer consists of cells indistinguishable from normal endothelium.

those animals which survived longer, fibroblasts were seen to replace the necrotic muscle (Fig. 34).

(c) Thrombus:

Histology confirmed the presence of thrombus in the atrial surface of the annulus and minimal evidence of thrombus on the ventricular side. Microscopy confirmed that the thrombus was antemortem; various stages of organisation were observed. No evidence of subacute bacterial endocarditis was found on any of the valves studied.

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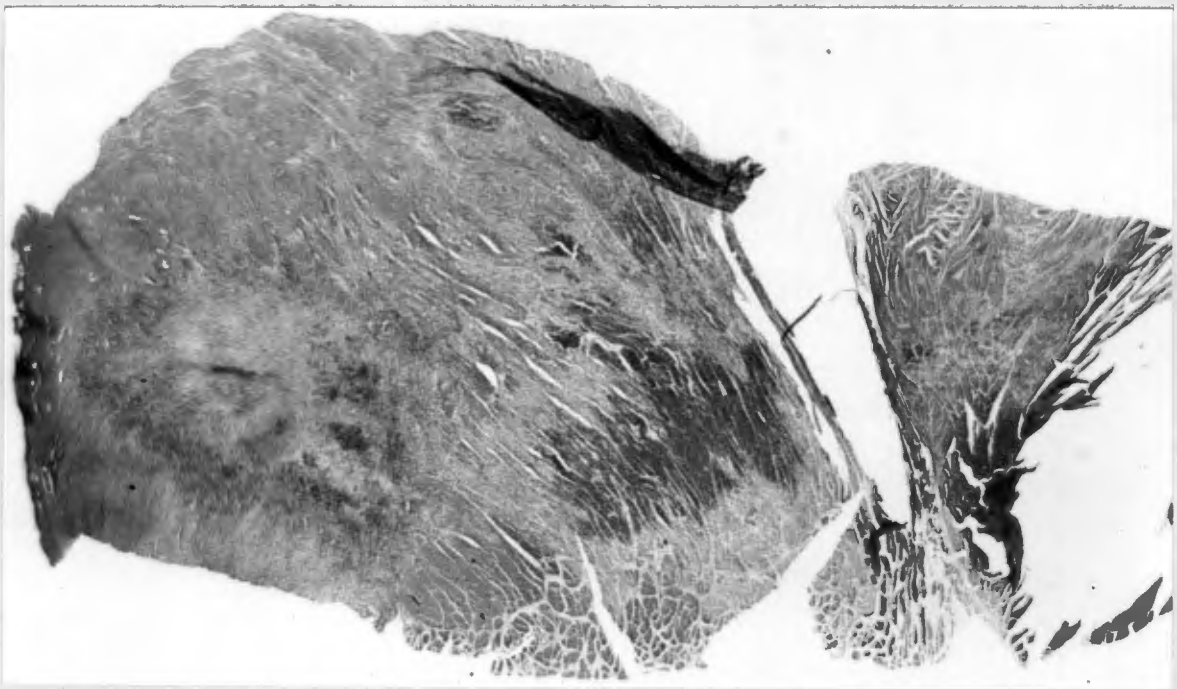
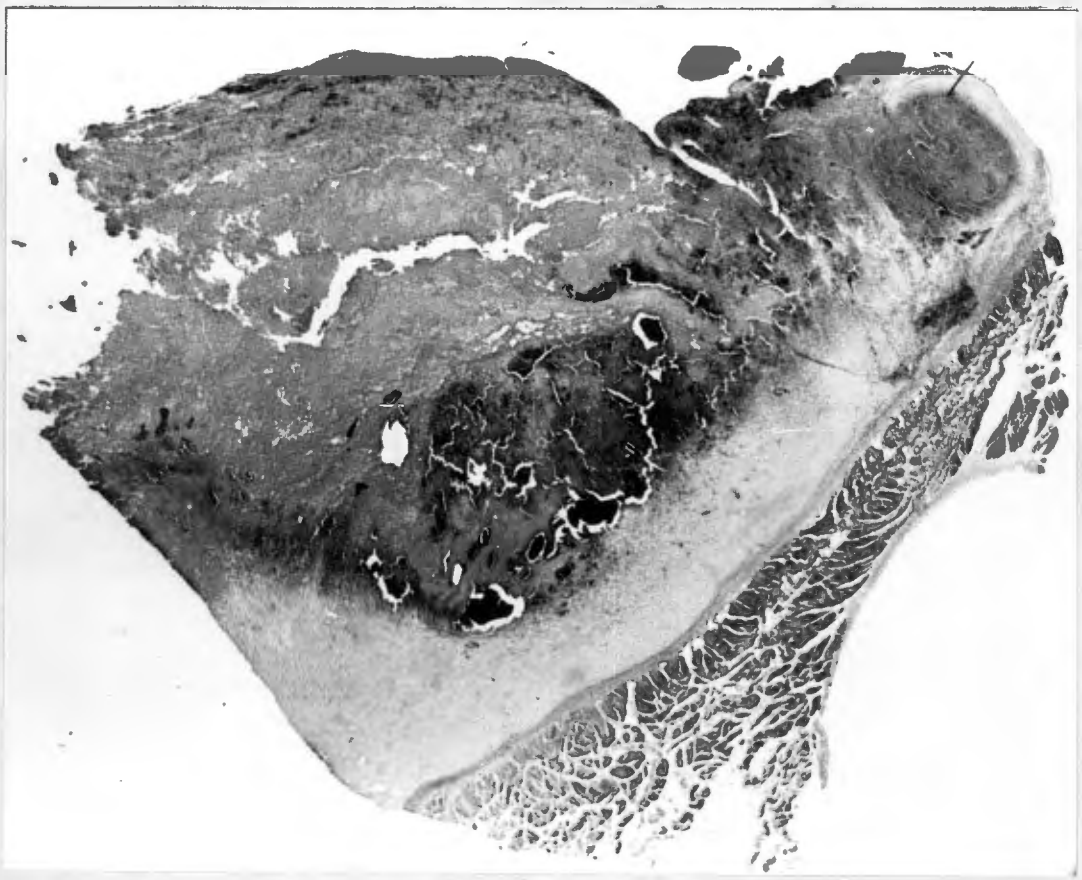
Fig. 34.



Histology of the mitral annulus of the same dog (see Fig. 33) demonstrating normal myocardium and areas where necrosis of the myocardium had occurred at the operative site. Fibroblasts can be seen replacing the necrotic muscle.

Fig. 35.



Histology of thrombus in atrium, annulus and ventricular surface of ventricle. The thrombus in the atrium demonstrates various stages of organisation. Note the absence of thrombus on the valvular surface.

RESULTS OF CATHETER STUDIES.

RESULTS OF CATHETER STUDIES.

Of the 8 dogs which survived for one month or more following mitral valve replacement with the U.C.T. prosthesis, 6 were catheterised to assess the haemodynamic function of the valve. The delay between operation and catheterisation ranged from 30 to 122 days.

In 5 of these dogs the prosthesis had been inserted in the subannular position, and in 1 case in the supra-annular position.

The results are detailed in Table 7. Sample tracings obtained in the control animal (Figs. 36 a - h) and in one of the experimental animals (Dog 2) (Figs. 37 a - g) are depicted.

FUNCTION OF PROSTHETIC VALVE.

All the animals studied showed a moderate degree of mitral stenosis with gradients across the mitral prosthesis ranging from 8 to 17 mm.Hg., average 11 mm.Hg. In all, this is accompanied by a significant elevation in wedge pressures, ranging from 14 to 26 mm.Hg (Hellems et al, 1948). In addition, in 3 animals (3,4 and 5) there was a significant rise in the mean pulmonary artery pressure.

There was no evidence of right ventricular failure as the venous pressure was normal in all cases.

The pulmonary vascular resistance was normal in all except Dog 6.

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Fig. 36 a. Control dog.

Normal right atrial trace.

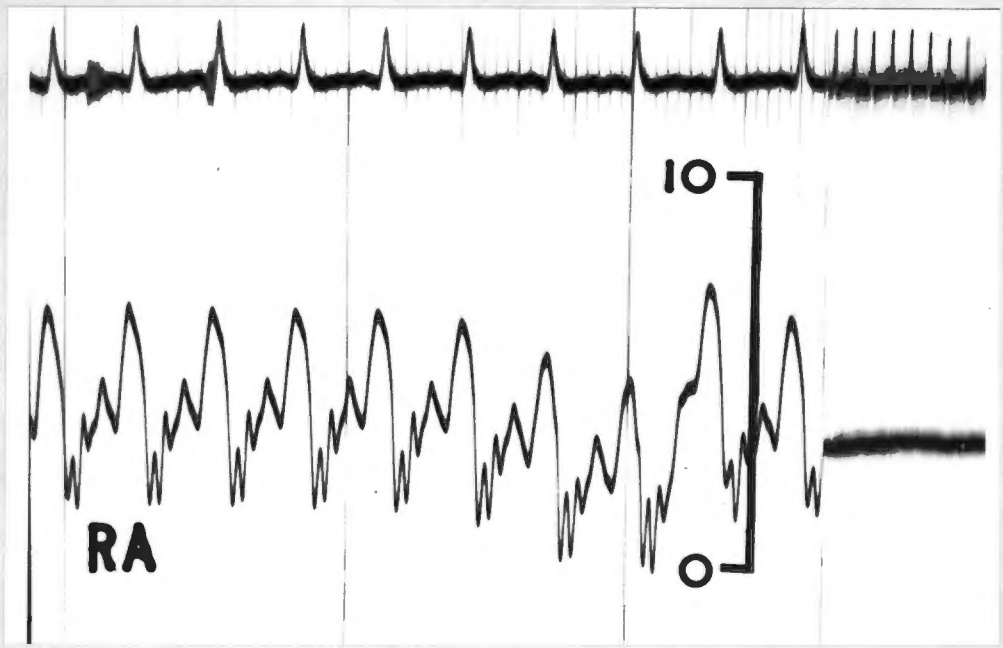


Fig. 36 b. Control Dog.

Normal right ventricular trace.

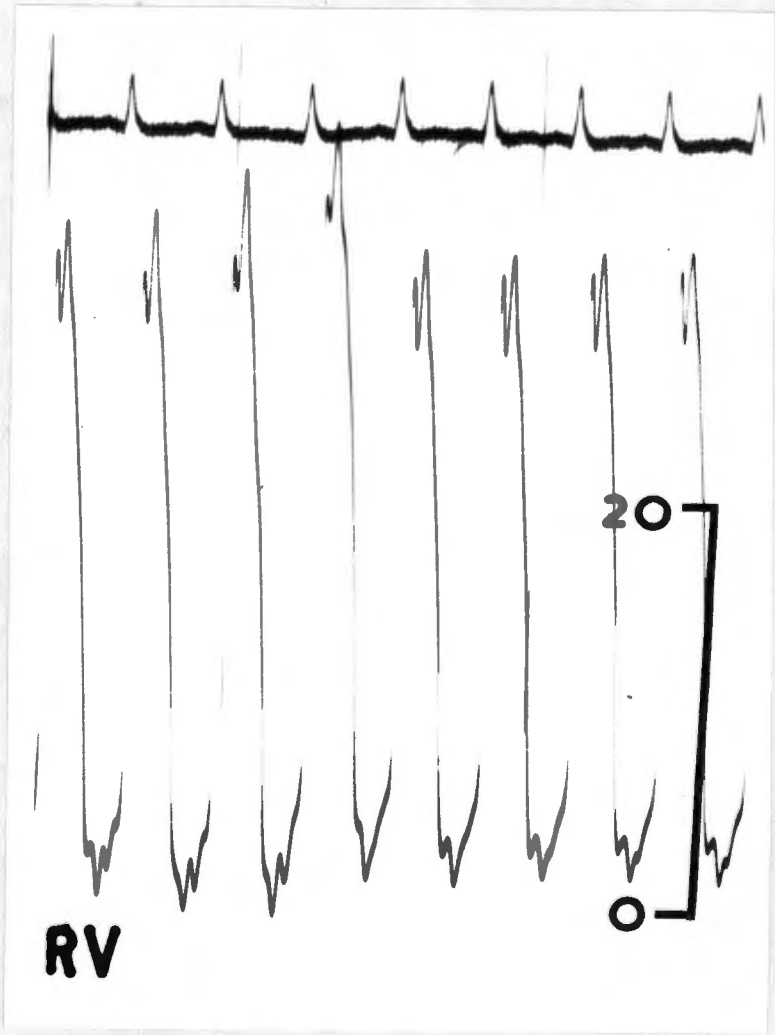
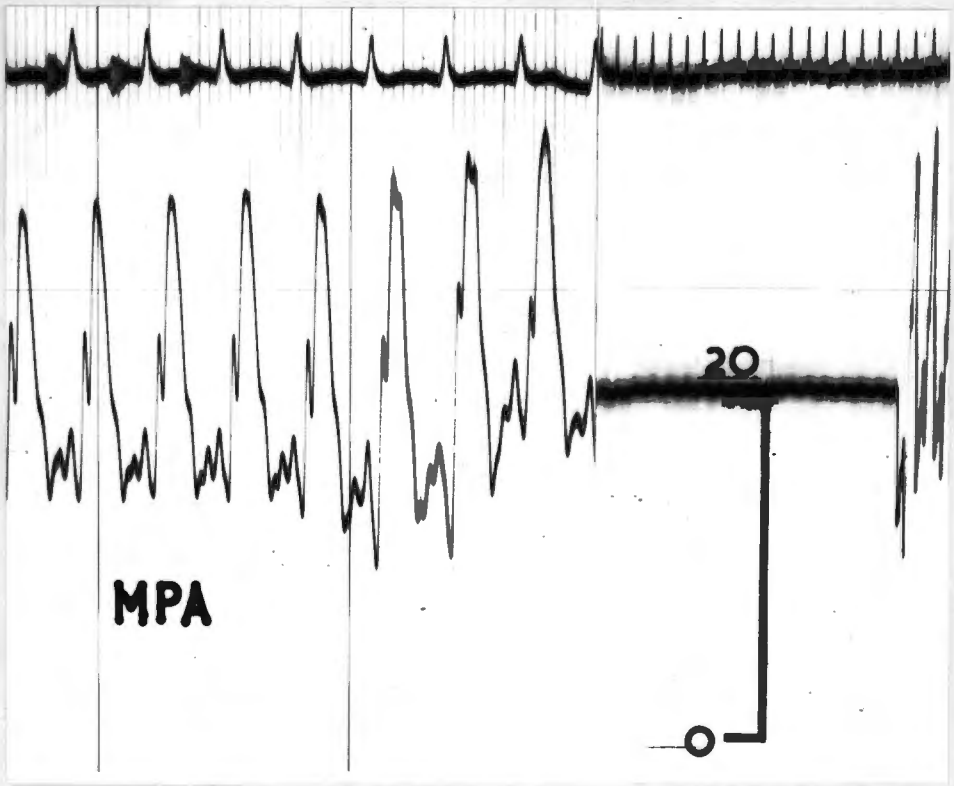


Fig. 36 c. Control Dog. Normal main pulmonary artery trace.



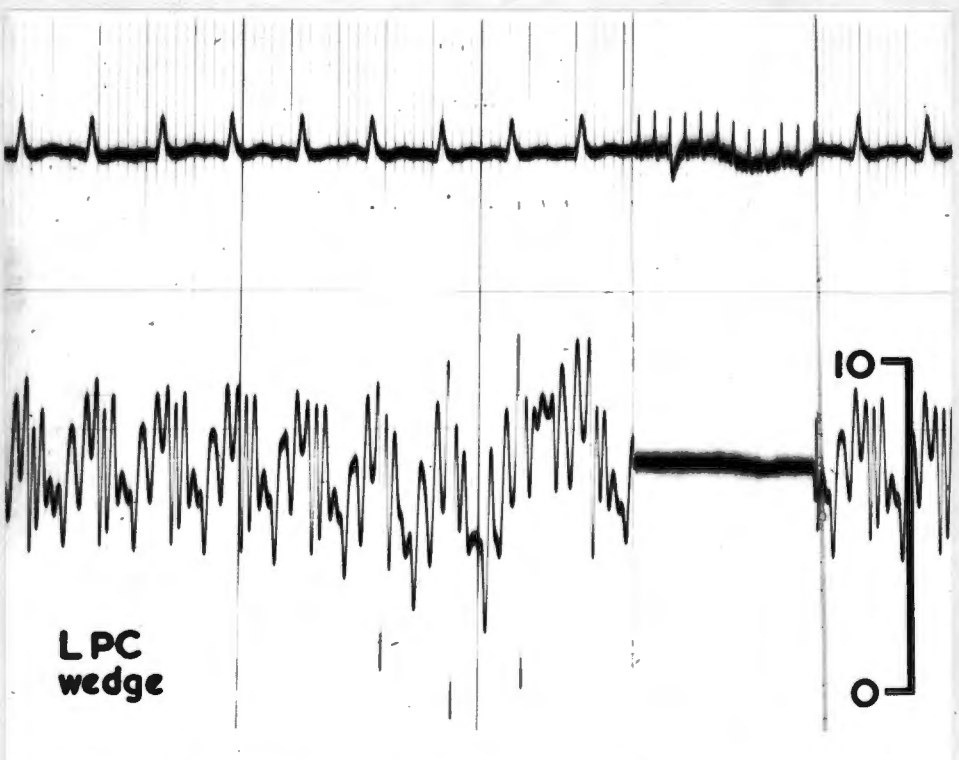


Fig. 36 d. Control Dog. Normal pulmonary capillary wedge pressure trace.

Fig. 36 e. Control Dog. "Snap free" on withdrawing from wedge in normal dog.

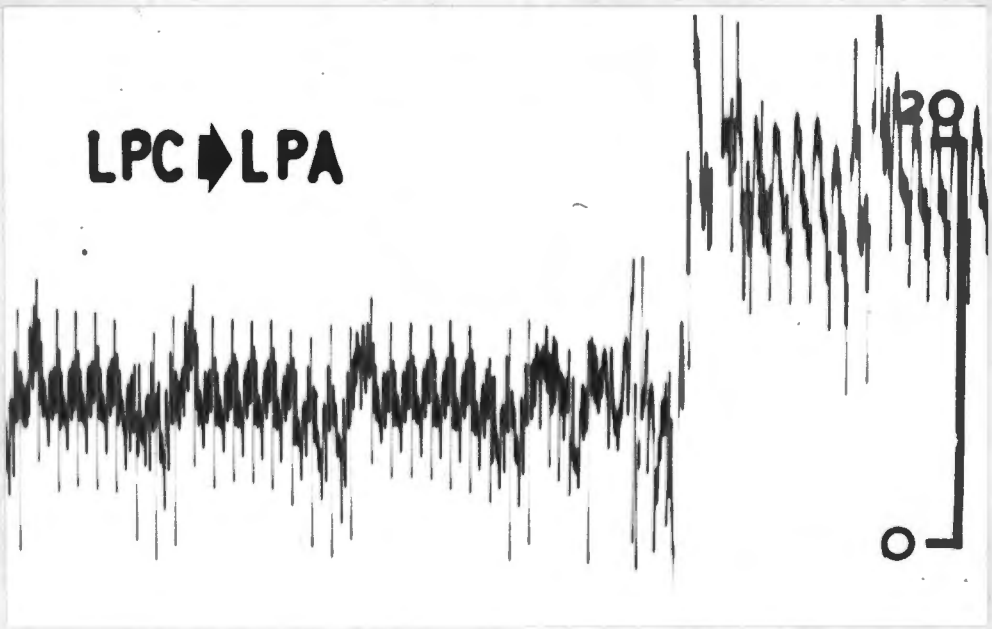


Fig. 36 f. Control Dog. Simultaneous tracings of left ventricle and wedge capillary in normal dog.

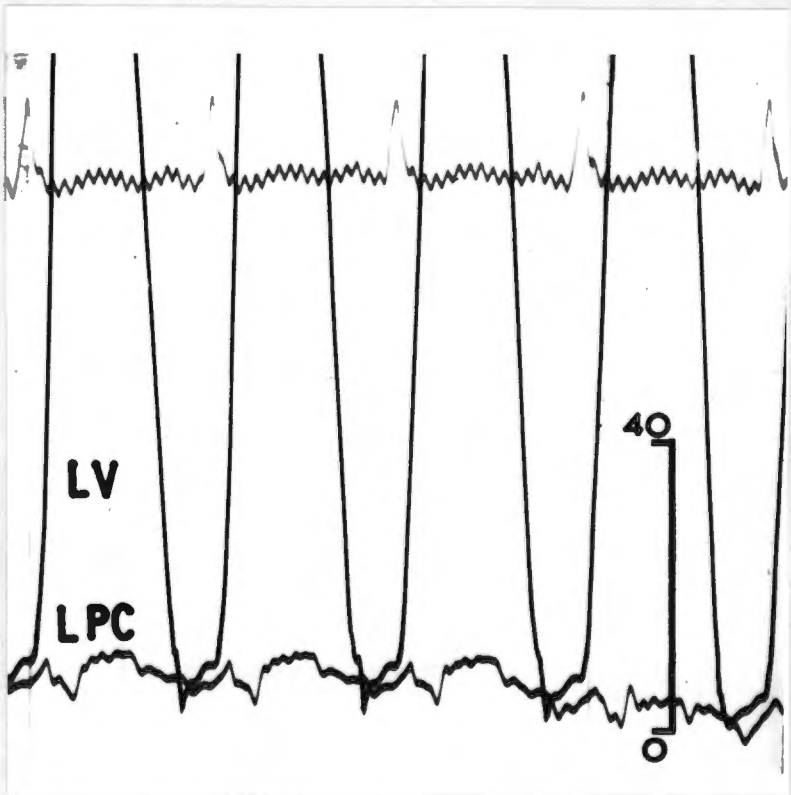


Fig. 36 g. Control Dog. Normal carotid artery pulse pressure.

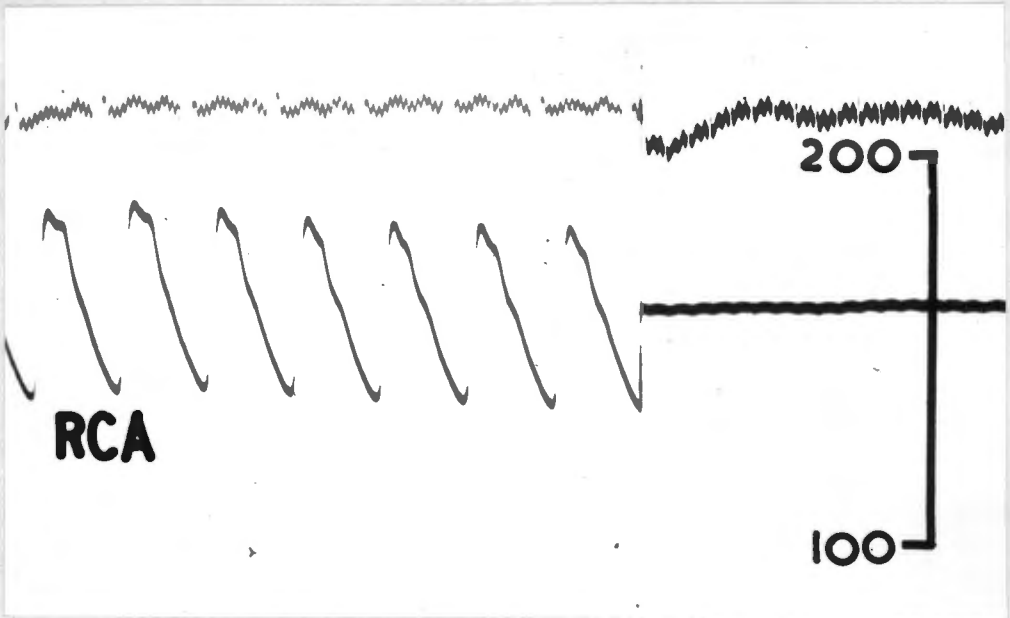
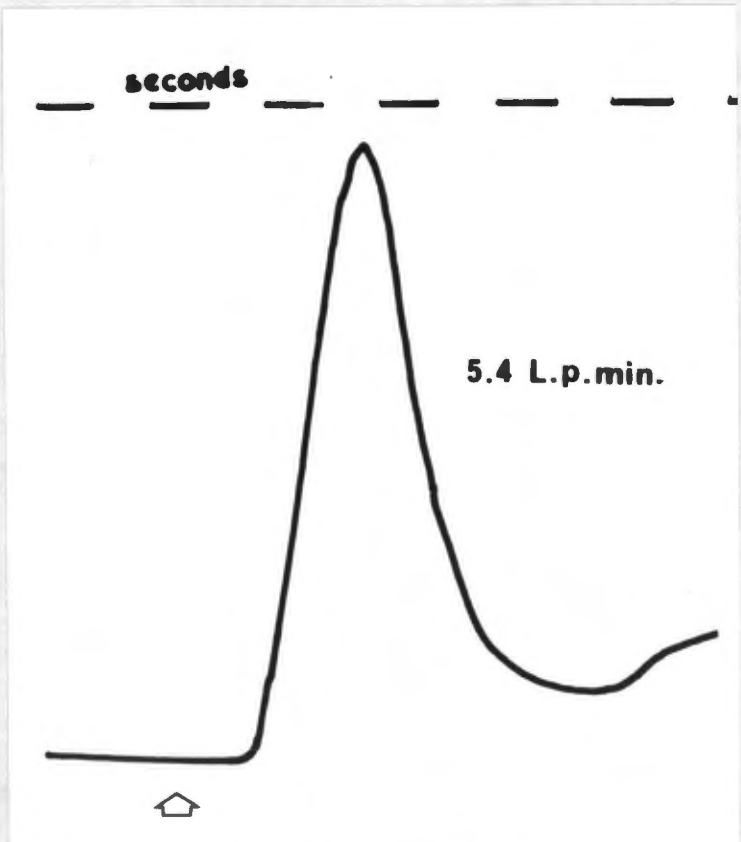


Fig. 36 h. Control Dog. Normal dye curve.



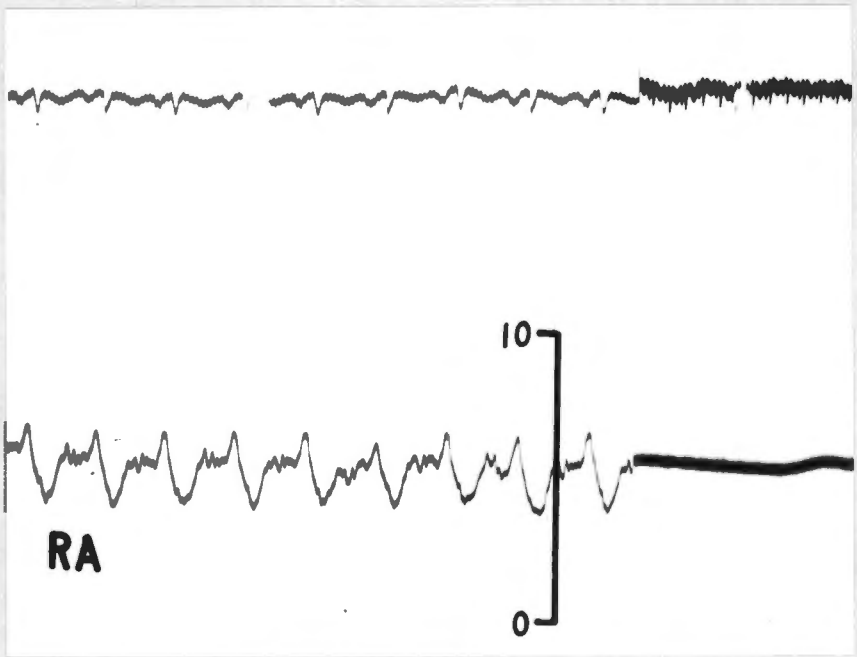


Fig. 37 a.
Dog No. 2.
Right atrial trace.

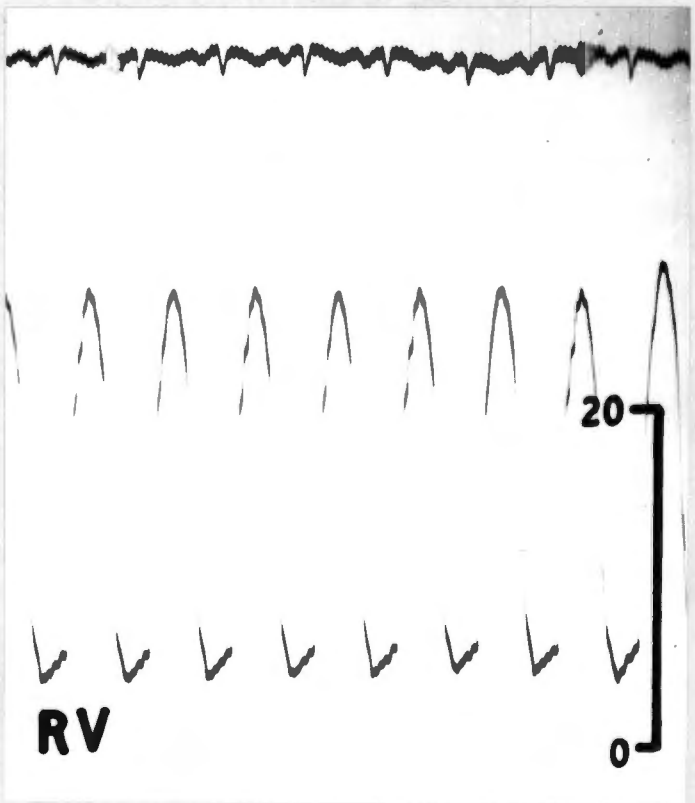


Fig. 37 b.
Dog No. 2.
Right ventricular trace.

Fig. 37 c. Dog. No. 2. Main pulmonary artery trace.

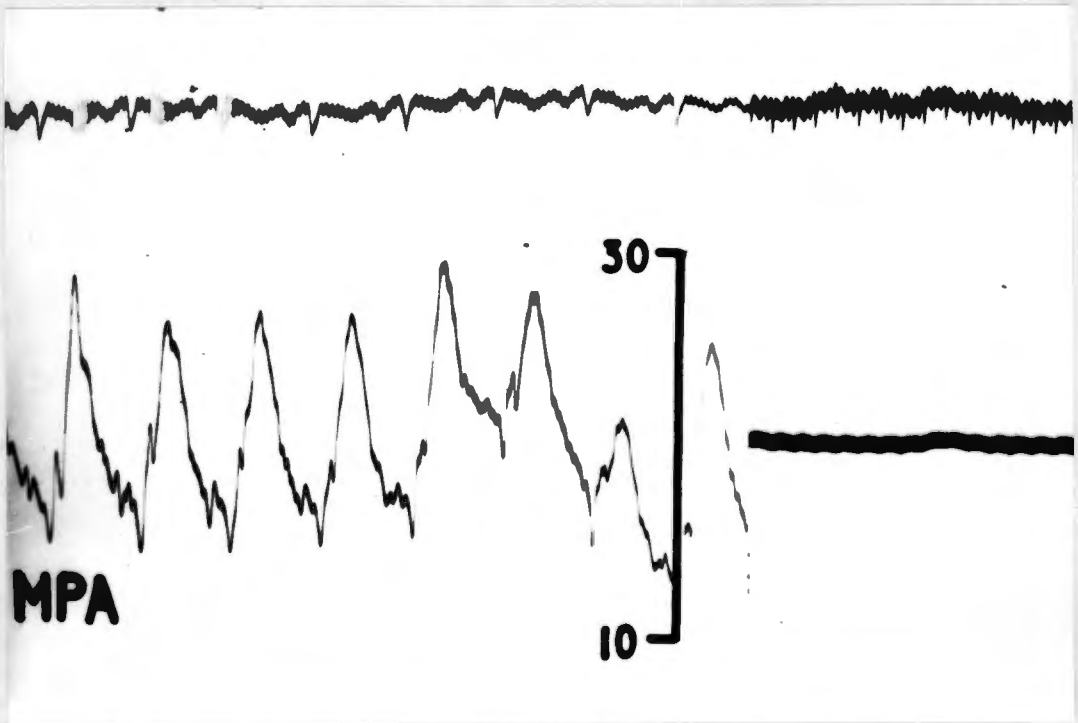


Fig. 37 d. Dog No. 2. Left ventricular and right pulmonary capillary wedge pressures.

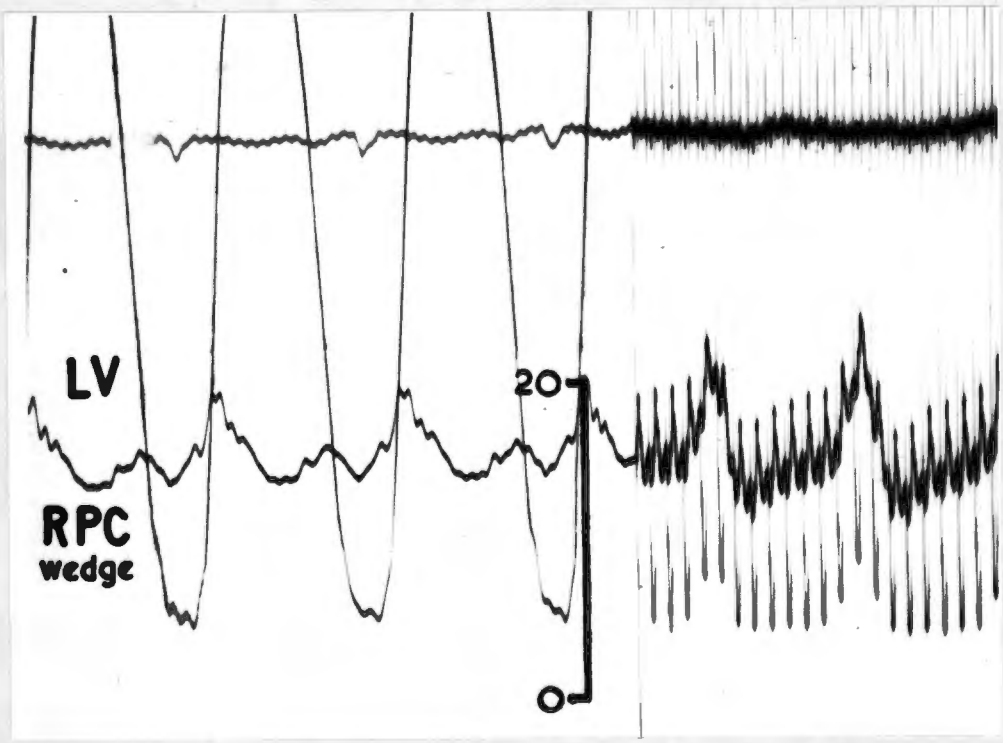
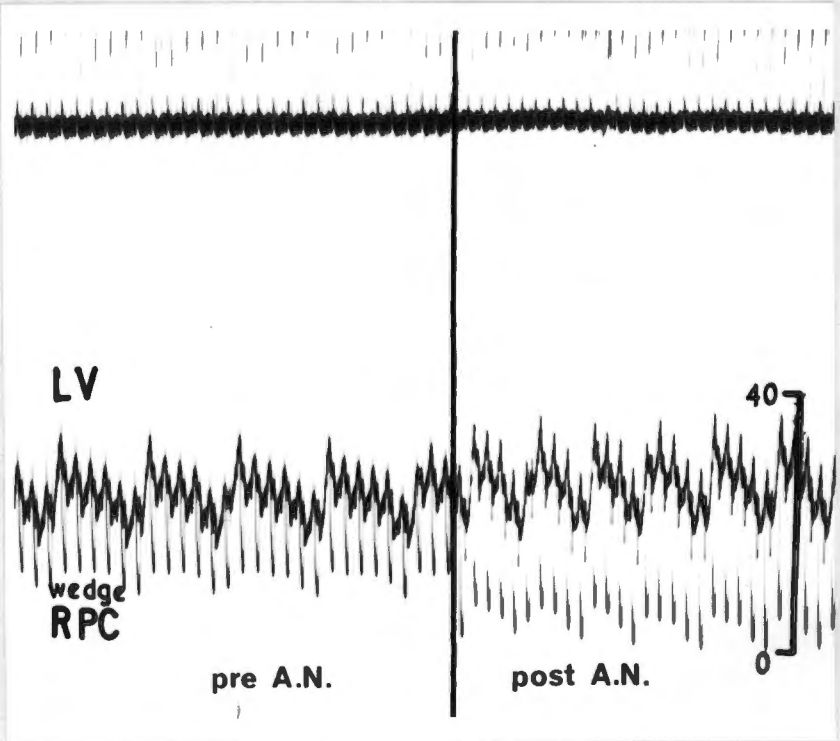


Fig. 37 e.

Dog No.2. Simultaneous tracing: right pulmonary wedge and left ventricle, before and after giving amyl nitrite.



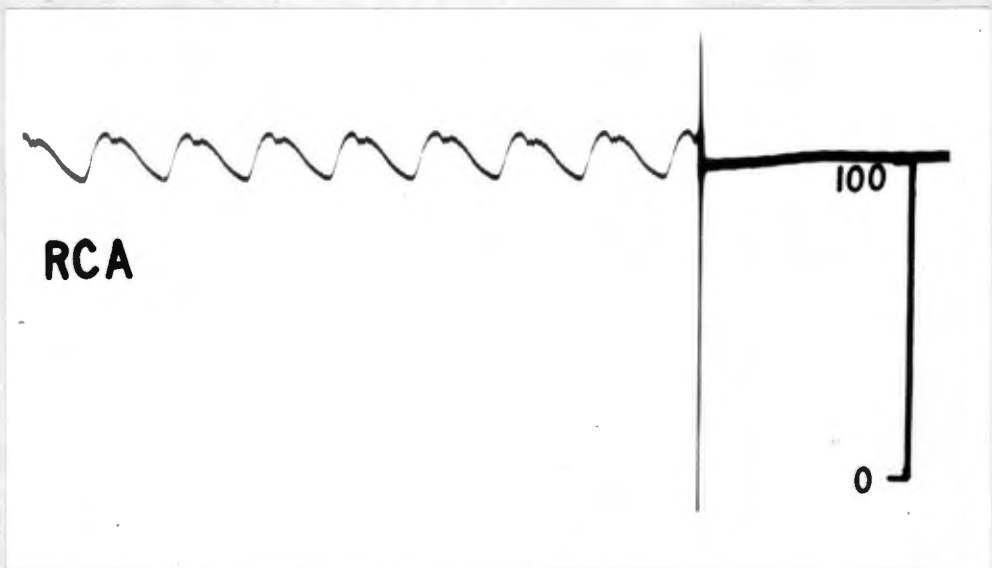
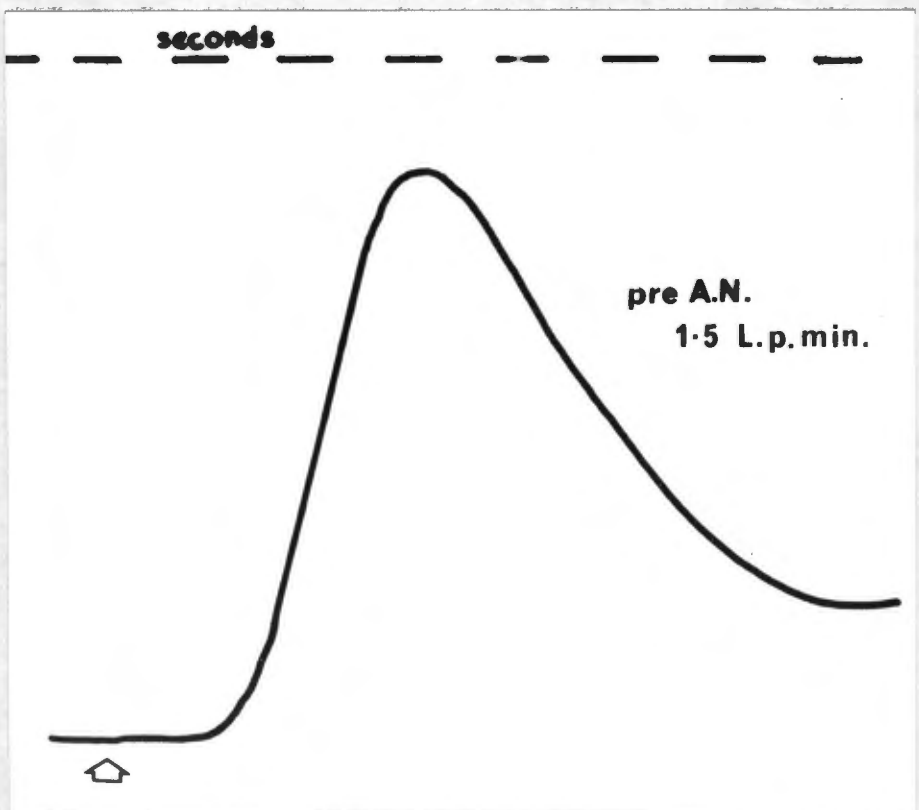


Fig. 37 f. Dog No. 2. Carotid artery pulse pressure.

Fig. 37 g.
Dog No. 2. Dye dilution curve.



CARDIAC OUTPUT.

The cardiac output in these dogs varied from 5.7 litres per minute to 1.05 litres per minute. The dogs could be divided into two categories, relating these output figures with body weight:

(1) 3 dogs had good cardiac output, the average being 198 cc. per minute per kilogram body weight (Dogs 1, 4 and 5). All three dogs were clinically fit at the time of catheterisation.

(2) 3 dogs had very poor cardiac output, the average being 93 cc. per minute per kilogram body weight (Dogs 2, 3 and 6). In comparison with those in the first group, these dogs were in poor condition when studied.

The dogs in the first group are all still alive and well, whereas all the dogs in the second group died soon after catheterisation, due to emboli and to chronic renal disease.

CALCULATED VALVE ORIFICE AREA.

All except Dog 6 evidenceda close correlation between the calculated valve orifice area (Table 9) and the effective area estimated by means of the formula propounded by Gorlin and Gorlin (1951). It is accepted that the equation might not apply accurately to these calculations, but a comparison between one animal and another is justified.

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Table 7.

DOG ▶		Control	1	2	3	4	5	6
OPERATION TO STUDY NUMBER OF DAYS		–	48	31	30	122	38	31
R.A. mean		6/2 3	6/3 5	7/4 6	7/3 5	6/2.5 4	10/1 3	3/1 2
R.V.		32/2-5	37/4-7	27/3-5	35/4-6	45/2-7	40/0-10	25/2-3
M.P.A. mean		31/14 20	37/24 19	27/16 20	35/21 30	45/20 35	40/15 30	25/15 19
P.C. wedge		8/4 6	27/18 22	16/11 14	30/24 26	31/21 25	35/15 25	15/10 13
L.V.		210/2-4	132/5-10	112/2-5	145/10-15	170/2-4	148/6-12	120/2-5
gradient		0	9	8	11	17	12	8
AORTA		220/135	132/160	112/90	145/115	170/100	148/100	120/85
Cardiac Output (rest) L/min.		5·4	4·5	2·0	1·5	5·7	3·8	1·05
WEIGHT Kg.	when operated	–	22	23	22	23	22	20
	when studied	23	23	18	15	27	20	16
Cardiac Output per Kg. (c.cs.)		244	195	112	100	210	190	66
P.V.R.		2·6	1·5	3·0	2·8	2·0	1·4	6·0
VALVE SIZE	calculated	–	1·65	1·41	1·41	1·89	1·65	1·41
	estimated	–	2·3	1·2	1·0	2·1	1·6	0·6
M.I.		–	0	0	0	0	0	0

Post-operative haemodynamic data in 6 dogs studied following replacement of the mitral valve with the U.C.T. prosthesis. One dog was also studied as a control.

LEFT VENTRICULAR FUNCTION. (Fig. 38).

The level of the systemic systolic blood pressure depends to a large extent on the stage of anaesthesia, especially when sodium pentothal is used as in our experiments, and also on the duration of operative manipulation.

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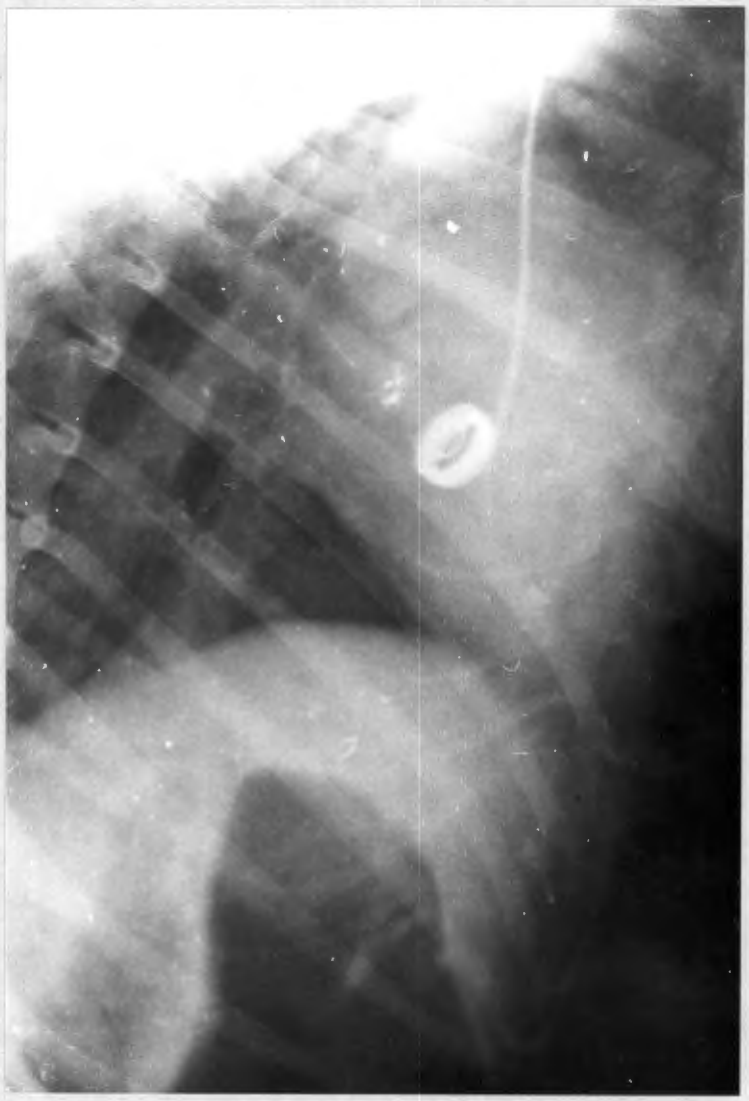
Fig. 38. X-ray photograph of dog in right anterior oblique position. A No. 6 Rodriques-Alvarez catheter is in the left ventricle. Dye has not yet been injected.



The level of the end diastolic pressure in the left ventricle is an indication of the efficiency of the left ventricular function. In our studies this was in the normal range, except in Dog No. 3. An abnormally shaped and functioning left ventricle was demonstrated in this animal on cine-angiocardiography (Fig. 39). Post mortem examination confirmed these findings (Fig. 30 b). The reason for

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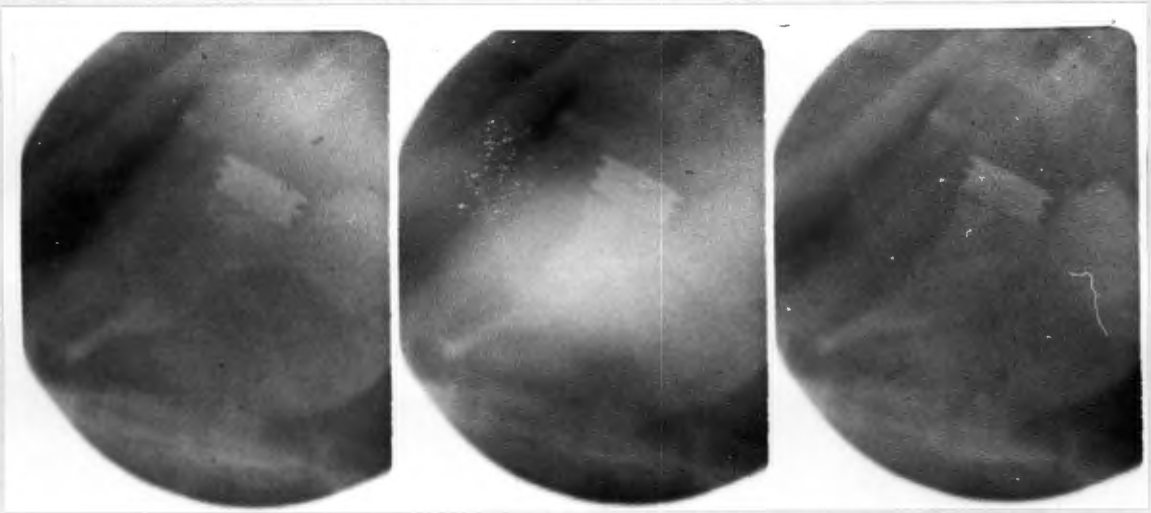
Fig. 39.

Dog No. 3. Cine-angiocardiography in right anterior oblique position. Note the abnormal left ventricular shape, competence of valve and no apparent outflow tract obstruction.



this is not clear, but does not appear to be related to mechanical obstruction of left ventricular outflow by the prosthesis.

All the other animals studied evidenced normally functioning left ventricles on cine-angiocardiography.

COMPETENCE OF THE PROSTHESIS.

Cine-angiocardiography was also used to study the competence of the prosthetic valve (Fig. 40). Any detectable mitral

incompetence produced through surgery resulted in the death of the dog within 24 hours (Tables 1 and 3). In 3 animals which died between 8 and 31 days after surgery death was directly attributable to mitral incompetence, (Tables 4 and 6). Cine-angiocardiography confirmed complete competence of the mitral prosthesis in all survivors.

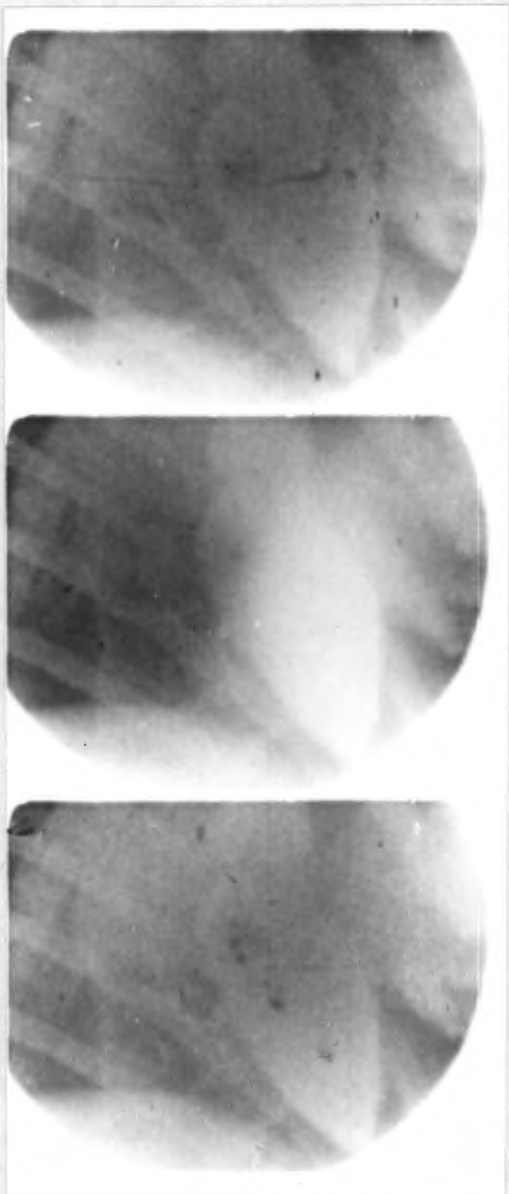


Fig. 40.
Dog No. 5. Cine-angiocardiogram. This shows no mitral incompetence.

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ATTEMPTS TO SIMULATE EXERCISE WITH AMYL NITRITE AND BODY HEATING.

In order to assess mitral valve function satisfactorily, it is essential to measure the haemodynamic changes produced by exercise. Attempts were made to raise the cardiac output by the inhalation of amyl nitrite and by body heating. The results were inconsistent.

The acceptable criterion of effective response is a rise in pulse rate. This was achieved in 2 animals (Dogs 2 and 5). In 3 there was no increase and in one temporary cardiac arrest developed and the experiment was not repeated. The animals which did respond with a tachycardia showed a rise in gradient, accompanied by an increase in cardiac output (Table 8).

Table 8.

DOG	PULSE RATE		GRADIENT		CARDIAC OUTPUT L/min.	
	Rest	Amyl Nit.	Rest	Amyl Nit.	Rest	Amyl Nitrite
2	200	220	11	20	1.5	2.2
5	170	210	12	14	3.8	5.1

Gradients and cardiac output before and after increase in pulse rate.

Table 9.

Comparison of diameter and calculated orifice areas of the canine and human U.C.T. mitral valve prostheses.

C A N INN E.			H U M A N.		
Mark II	Internal Diameter	Calculated Orifice Area		Internal Diameter	Calculated Orifice Area
a	14 mm.	1.41 sq.cm.	Mark II	21 mm.	3.2 sq.cm.
b	16 mm.	1.89 sq.cm.		23 mm.	4.1 sq.cm.
				26 mm.	5.3 sq.cm.
Mark III	15 mm.	1.65 sq.cm.	Mark III	21 mm.	3.4 sq.cm.
				24 mm.	4.5 sq.cm.
				27 mm.	5.8 sq.cm.

DISCUSSION.

D I S C U S S I O N.

The distressing incidence of emboli in humans following total mitral valve replacement with the U.C.T. lenticular prosthesis stressed the need for a full experimental evaluation of this valve.

Results from other centres (Kernan et al, 1957; Starr, 1960) show that it is exceptional for a dog to survive for more than a few weeks following insertion of a mitral prosthesis. Clark reported a 3% one month survival in a review of the results from 19 different centres (representing 557 dogs) in 1964. In the vast majority, the development of thrombus on the atrial side of the prosthesis - occluding the orifice and interfering with valve function - was the cause of death. The great tendency for thrombosis on prosthetic valves placed in dogs makes this animal eminently suitable for the study of this common and serious complication. Any procedure developed experimentally which reduces the incidence of thrombosis in the dog may, without hesitation, be applied clinically with a reasonable expectation of reduction in the incidence of thrombus.

In Group A of this experimental investigation, the U.C.T. Mark II mitral prosthesis was inserted in the supra-annular position. This meant that the Dacron suture ring, the inner steel ring and the steel suspension arm projected slightly into the atrial cavity, thus forming part of the atrial wall. Follow up showed that all these animals died within 8 days of surgery. In the nine surviving longer than 36 hours, obstructive thrombus of the valve orifice resulted

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in acute left heart failure leading to death in every case. At post mortem, the striking finding was the massive thrombus which was invariably present on the atrial side of the artificial valve. There was minimal thrombosis on the ventricular side and what was seen there had originated on the atrial aspect and extended through the valve opening. These findings were in keeping with those reported by Ellis and Balbalian (1958) and by Starr (1960), Gross et al (1963), and Cartwright et al (1964).

In the surgical treatment of rheumatic mitral valve disease the cardiac surgeon is faced with the fact that thrombo-embolic complications are a feature of the natural history of this condition. The incidence increases with the onset of congestive cardiac failure and atrial fibrillation (Askey and Bernstein, 1960). Replacement of the diseased mitral valve by means of a prosthesis relieves (or often only partially relieves) the mechanical lesion. The pre-existing pathological anatomy of the left atrium remains essentially unaltered. In this environment, already predisposed to thrombosis, is placed a prosthesis manufactured from foreign materials. Thus it is not surprising that the resultant turbulence in blood flow and operative trauma associated with the procedure increase the incidence of thrombo-embolic complications.

On the other hand, the left ventricle behaves quite differently. Rheumatic involvement of its musculature, obstruction of its outflow tract, and left ventricular failure, do not give rise to the same high incidence of embolic complications as they do when the same circumstances operate in the left atrium.

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Clinical experience has further substantiated this finding, in that thrombo-embolic episodes are at least five times more common in mitral than in aortic valve replacements (Effler et al, 1965; Barnard et al, 1965). The precise reason for this difference is not clear, but it probable stems from the different haemodynamic conditions existing in the two chambers.

It would appear reasonable to conclude that, if the mitral prosthesis is placed in such a way that it is mainly exposed to the left ventricular environment, the thrombo-embolic problems will be reduced.

In experimental Group B, it was thus decided to insert the mitral prosthesis in such a way to expose as little as possible of the valve to the left atrial environment. In the subannular position, the bulk of the valve is removed from the atrium. Fortunately, the U.C.T. prosthesis (without a bulky intraventricular mechanism) lends itself well to this mode of insertion. Using a prosthesis with a large cage, the chances of septal trauma and ventricular outflow obstruction will be increased by subannular insertion.

The results achieved in Group B, where the prosthesis was placed in the left ventricle, subannularly, showed a definite reduction in the incidence of massive thrombus.

Five dogs died between 24 hours and 12 days after operation but in only two was thrombosis the sole cause of death. These 2 animals had clinical courses, and showed post mortem findings, very

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similar to those noted in Group A. Although the bulk of the prosthesis was exposed to the ventricular environment, however, this was free of thrombus whereas thrombus was present in the atrium, appearing to arise from the areas of maximal operative trauma.

Two dogs which survived for more than one month were studied at post mortem. They did not die as a result of massive occlusive thrombosis. Here again the ventricle was free of thrombus and the Dacron suture ring was covered with healthy endothelium. Thrombus was present in the left atrium but was not extensive enough to cause valve obstruction.

Four dogs from Group B are still alive and well from four to six months after operation.

A comparison between Groups A and B clearly shows the better results achieved following subannular insertion of the mitral prosthesis. In Group A, all 9 dogs surviving more than 36 hours after surgery died within 8 days as a result of occlusive thrombosis. In Group B, 11 dogs survived longer than 24 hours; in only 2 was occlusive thrombosis the sole causeof death, 6 survived longer than one month and 4 are still alive and thriving 4 to 6 months after operation.

The operative procedure in the two groups was essentially the same. If anything, subannular insertion of the valve should produce more trauma to the atrial wall, being the more difficult procedure.

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The prostheses used in the two groups were similar.

The only possible explanation for the better results obtained in Group B must be the placing of the prosthesis in the subannular position, where it is exposed to the ventricular environment.

Subannular insertion of the valve has an additional advantage in that the prosthetic cuff rests on the under-surface of the mitral annulus, where each systole tends to seat it more firmly. In this way, the systolic strain is taken off the sutures and valve dislodgment is much less likely to occur. On the other hand, when the valve cuff is fixed with its edge at the level of the annulus, or above it, each systolic contraction tends to dislodge the prosthesis. The result is that those parts of the prosthesis not held firmly in contact with the annulus tend to move away from it, permitting leakage.

The poor clinical results reported by the use of anticoagulant therapy in the prevention of thrombus stimulated the study of the effects of intravenous streptokinase. Our experience showed that thrombus started on the valve as early as 36 hours following insertion. The results obtained in Group C, where streptokinase was administered after valve replacement, showed a delay in thrombus formation. However, in those animals which survived more than 2 weeks, multiple peripheral emboli occurred, resulting in death. The hearts of these dogs, examined at post mortem, were characterised by the friable appearance of the thrombus on the prosthesis.

It appeared that streptokinase not only partially digests thrombus, but that it also interferes with the normal healing

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process, i.e. organisation of the thrombus. The thrombus itself remains soft and friable, producing multiple emboli. The findings in these experiments suggest that streptokinase partially digests the thrombus already formed on the prosthesis, thus preventing serious obstruction. However, this form of therapy may increase the risk of smaller emboli, by preventing the natural healing process.

Histology of the various organs examined confirmed the macroscopic findings. However, the possibility that thrombosis could have been the result of infection was eliminated.

In these dogs the prosthetic valve was placed in the mitral area of a previously normal heart. In patients, on the other hand, there is previous long-standing cardiac failure, often associated with severe myocardial damage. Disease of other valves and pulmonary complications are frequently present.

Haemodynamic studies (though not comparable with those done clinically by Beck et al in 1965) provided an opportunity for the assessment of the U.C.T. prosthesis in a heart which was normal before operation. The studies performed in the post-operative period showed significant mitral stenosis in all the animals investigated. Those dogs which appeared well and thriving post-operatively all had good cardiac outputs (average 193 cc./kg./min.). The canine size U.C.T. mitral prosthesis used in a normal heart is thus capable of a relatively high cardiac output, at the expense of a moderate gradient only. It is reasonable to assume that if it were technically

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possible to insert a larger prosthesis, a similarly good cardiac output could be achieved with a lower gradient.

The catheter findings revealed a relatively close correlation between the directly measured orifice area and the effective orifice area, in these experimental conditions. This is in direct contrast to the findings reported by Beck et al (1965) after a clinical study. The explanation for this must lie in the relatively high gradients found experimentally as compared with the clinical findings.

Cine-angiocardiography confirmed that the U.C.T. prosthesis was competent and that no aortic outflow obstruction was produced when this valve was placed in the subannular position.

SUMMARY AND CONCLUSIONS.

SUMMARY AND CONCLUSIONS.

At the time when this experimental study was concluded, 51 patients had undergone mitral valve replacement with the University of Cape Town lenticular prosthesis since its introduction in 1962. Of these, 49 have been followed up for at least 3 months post-operatively. Clinically the prosthesis has proved durable (Barnard et al, 1965) and its haemodynamic efficiency has been confirmed by catheter study (Beck et al, 1965). However, in spite of certain modifications in valve design, the incidence of post-operative embolus has remained alarming.

Thrombo-embolism after mitral valve replacement is a major complication which has also been the experience of others, both experimentally (Ellis and Balbalian, 1958; Starr, 1960) and clinically (Björk and Malers, 1964; Herr et al, 1965). There is general agreement that total mitral valve replacement should be recommended only in patients to whom medical treatment no longer offers any relief, and where no other surgical procedure will restore valve function (Barnard and Schrire, 1961; Barnard et al, 1963).

An experimental study was designed to investigate thrombus formation after total mitral valve replacement with the U.C.T. prosthesis in the canine heart.

Closely simulating clinical conditions, using extracorporeal circulation with haemodilution and moderate hypothermia, total mitral

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replacement was performed in 39 dogs. Studying different techniques for the insertion of the prosthesis, and the effect of the post-operative administration of streptokinase to dissolve thrombus, there were three experimental groups:

Group A (16 dogs) - Supra-annular placement,

Group B (17 dogs) - Subannular placement,

Group C (6 dogs) - Supra-annular insertion of the prosthesis with post-operative streptokinase.

No anticoagulant therapy was used post-operatively. Only the animals which lived longer than 24 hours after surgery were studied. Catheter studies and cine-angiocardiography were performed in 6 long-term survivors.

In Group A there were 10 survivors. One animal died after 36 hours, due to air embolism. On examination, fibrin thrombus was already present on the atrial side of the prosthesis, at this early stage. Of the remaining 9 survivors, none lived longer than 8 days. The clinical course was similar in all: increasing dyspnoea and progressing signs of congestive cardiac failure, which rapidly led to death.

Post mortem examination confirmed the presence of pulmonary oedema and pleural effusion. The left atrium in each case was filled with a massive thrombus, originating at the suture ring and extending across the prosthesis to occlude the orifice of the valve. In contrast, the ventricular aspect was quite free of thrombus, any that could be seen having originated in the atrium and extended through the orifice.

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In Group B there were 11 survivors. One dog succumbed after 36 hours, due to air embolism. On examination post mortem, no thrombus was present in the left atrium. Of the remaining 10 survivors, 4 died within 12 days - 2 as a result of thrombus arising from areas of trauma to the left atrial wall and occluding the orifice, and 2 due to disruption of sutures and mitral incompetence. The other 6 dogs in Group B survived for a month or longer. Two of these have now succumbed, one being sacrificed on the 31st post-operative day and the other dying as a result of bilateral chronic renal disease on the 40th post-operative day.

Post mortem examination of the hearts of these 2 dogs revealed a well organised thrombus on the posterior left atrial wall. The ventricular aspect of the prosthesis was covered with a shiny, healthy endothelium, but there was no evidence of thrombosis.

The remaining 4 dogs in Group B are still fit and thriving, four to six months after operation.

In Group C there were 5 survivors. Three dogs died within 12 days, due to occlusive thrombosis. The remaining 2 dogs died on the 31st post-operative day, as a result of disruption of the prosthesis and multiple emboli. In all hearts examined the most striking finding was the friability of the thrombus on the prosthesis and the delay in normal healing. This delay in healing was also evident in the thoracic incision. The lack of normal invasion of the Dacron suture ring and organisation of the thrombus, compared with the findings in survivors in the previous groups, resulted in

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dislodgment of multiple emboli to the spleen and kidneys.

Catheter studies and cine-angiocardiography were performed on six dogs which survived more than one month. The catheter studies confirmed the efficiency of the UCT lenticular mitral prosthesis. No evidence of aortic outflow tract obstruction was evident when the prosthesis was inserted in the subannular position.

The results indicate that a definite reduction in thrombo-embolic complications may be expected if the bulk of the prosthetic mitral valve is placed in the left ventricle, rather than in the customary left atrial position. The administration of streptokinase post-operatively tends to delay thrombosis but does not prevent it.

At present, the more general use of total mitral valve replacement is limited by the high incidence of thrombo-embolic complications. In view of this problem, most workers agree that total mitral valve replacement must be reserved for the severely incapacitated patient only, and only if no other procedure is technically possible.

The results of this study indicate that subannular placement of the prosthesis will diminish the incidence of post-operative emboli to within more acceptable limits. If this is achieved, total mitral valve replacement could be recommended in place of the unsatisfactory plastic procedures now performed.

Haemodynamic study confirmed the efficiency of the U.C.T. mitral prosthesis in the heart of a normal dog and, in spite of the

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small orifice of the canine valve, excellent cardiac output was achieved.

It is possible that, if serious complications following total mitral valve replacement can be reduced to the minimum - knowing and even improving the efficiency of the prosthesis in a normal heart - better long-term results could be obtained by recommending mitral valve replacement at an earlier stage of the natural history of the disease, before other severe and irreversible myocardial and pulmonary sequelae occur.

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