Biologic Valves
Their Performance and Prospects

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For instance it has become a bad habit, which we all share, that when talking about heart-valve prostheses we tend to give the results and extoll the virtues of model A and then later, when problems arise with it, present instead only the trouble-free results from model B (fig. 1). This sequence then continues for a number of years so that by a combination of increasing experience and improved technical developments one is finally able to present the recent and excellent trouble-free results with model C or D. At the same time, if pressed, one can acknowledge like a man the shortcomings of the earlier model A, "which of course is no longer used."

Yet, if one looks closely at the various prosthetic valves there has been little fundamental design change, just like the new automobile which appears annually with a different metallic skin covering the same familiar mechanics.

Again, with say homograft aortic valves, nothing fundamental has changed in the design principle since it was introduced several million years ago, but there has been a little bit of juggling with the preparation and storage media in which they are immersed. This again introduces the temptation to give only recent good results with the latest storage preparation.

Since the aortic homograft among biologic valves has had the longest run, one can try to assess how in our hands it matches the results with mechanical prostheses reported from other centers over a similar period of time. Also one can look at some alternative biologic valves which we have used and see whether

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they offer any improved performance or prospects.

I know that the aggregation of different mechanical valves under the term mechanical 'prosthesis' may be objected to, particularly by surgeons, on the grounds that their own particular valve variation has superior qualities which make it unique. Nevertheless, whatever their trade description, all mechanical valves have in common a central occlusive device and a fixed-orifice, rigid sewing ring for attachment. As a product of man's inventive genius and technical achievement they provide very fine examples. Moreover they are easily sterilized and readily obtainable in varying sizes.

Taking these factors into consideration, together with the many detailed reports and the analyses of their clinical application over the past decade,1-6 one may reasonably take the view that since most valve-replacement surgery is at any rate palliative we should accept mechanical prosthetic valves as standard therapy and stop fretting over biologic alternatives. If we were interested only in mortality statistics this would be a wholly acceptable attitude, but as doctors we should also be concerned with the duration and quality of life our postoperative patients can look forward to once the operation is over.

In 1962 I reported the use of a nonliving homograft as an aortic valve substitute7 and since that time there has been a parallel development with mechanical prosthesis but on a much smaller scale. Nevertheless biologic valves in various guises continue to be used in a number of centers,8-11 and a sufficient number have now been studied to make some assessment of them at least in the aortic area.

My initial preference for a homograft valve was influenced by the fact that it incorporated perfect design and structural features, and as Gordon Murray of Toronto had shown12 it could certainly function in the descending aorta (fig. 2).

There were and still are other theoretical reasons which have made me continue to use

Figure 1

The popularity of a particular valve modification is often related to the time it has been in clinical use.
and evaluate these valves. These relate chiefly to the knowledge that the valves in the normal heart are the product of several million years of evolutionary development. Whatever the present disadvantages of these when used as replacements, it seems reasonable that human valves or those based on the natural design are unlikely to be bettered in a few years of workshop development based on simple hydraulic and engineering concepts.

Having made these preliminary observations I would submit that a primary consideration in deciding to use a particular valve should be that the immediate risk of mortality attendant upon its use should be comparable with other available methods of treatment in similar groups of patients.

Between the years 1963 and 1971, a consecutive series of 282 aortic homograft replacements were inserted by me at the National Heart Hospital in London for dominant aortic valve disease, and the survivors have been closely followed. This series includes several modifications in surgical technic and three separate methods of valve preparation.

Figure 2

Comparison of the central-flow biologic valve with the centrally obstructive prosthetic device.

Figure 3

Overall hospital mortality at the National Heart Hospital to mid 1971, 15.3 and 5.3% over the past 4 years.

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Figure 4

Three published homograft series of aortic valve replacements compared with four recent prosthetic series.
Of these 282 patients, 43 died within 30 days of surgery, giving an overall hospital mortality of 15.3% (fig. 3). As has been the experience in most series, this hospital mortality has fallen steadily, and over the past four years has averaged 5.3%. A comparison of four fairly recently published groups of mechanical valve replacements inserted over a similar period of time together with three groups of homograft replacements shows comparable figures, but with the bias slightly in favor of homografts (fig. 4).

Factors relating to mortality and the valves’ early function therefore do not influence me strongly toward a homograft or a mechanical prosthesis. Of more immediate concern to the patient and the cardiologist is the subsequent function of the valve. Here we as surgeons owe a collective debt of gratitude to Dwight McGoon of the Mayo Clinic for encouraging the need to present our data if possible as an actuarial curve.13 This expresses our results as a percentage of those patients at risk over a given period of time and is a convenient way of indicating survivors and their good or bad results in comparable form.

We have prepared a curve for the series of 419 patients submitted to homograft aortic valve replacement at the National Heart Hospital and Guy’s Hospital both by myself and my collaborators, and I believe it complies as nearly as possible to the criteria laid down in McGoon’s paper. A mean survival curve for five separate series of prosthetic aortic valves published from other centers has been added with some actuarial poetic licence as a second curve, and the results have been both sobering and enlightening (fig. 5).

For instance, we had expected to be able to show that the homograft survival prospects were better than those for the mechanical valves. In fact it appears that in this experience there is little to choose between the two types of valve substitute over this period of time but that whatever form of valve replacement is used the result is a good deal better than the outlook for the natural history of aortic stenosis shown on the same graph.

However, there are currently a number of ways of presenting survivors and survivor statistics. For instance the previously mentioned series of 282 cases operated upon by me and for which hard data are available can be shown in a very favorable light by presenting and following only the 235 survivors. This is achieved by moving the scale to the right by 1 month, which effectively excludes the operative mortality and gives the curve a substantial lift up.

![Figure 5](http://circ.ahajournals.org/)

**Figure 5**

Survivor curve for homograft series from Guy’s Hospital and the National Heart Hospital compared with a mean survivor curve for five prosthetic valve series. The survivor curve for untreated aortic stenosis is also included.

![Figure 6](http://circ.ahajournals.org/)

**Figure 6**

Personal series presented as a survivor curve. Top curve considers only survivors excluding operative mortality, while bottom curve includes all patients operated upon.
Survivor curve showing valve survival, that is the number of patients surviving with their original valve in place. Again the top curve excludes operative mortality. Note accelerated valve degeneration around 5 years.

Looking at the top curve you then see that 85% of these surviving patients continue to survive at the end of 7-8 years (fig. 6). However, if we take into consideration the 15.3% early operative deaths then the survivors from the whole group of 282 cases operated upon would be 70 and not 85% at the end of this period.

Again a similar curve of survivors can be constructed to take into account also the fate of the valve. We then see that of the 235 survivors 74% continue to survive with their original homograft valve in place (fig. 7). However, if we consider the whole group and the operative mortality and not only the survivors, then only 61% of the original patients survive with their homograft valve, which is a figure much nearer to the original actuarial curve covering the 419 patients from two hospital groups. These figures are not meant to confuse, and to the best of my knowledge are accurate. They simply serve to indicate how the same results can well be presented in very different forms and indicate the need for an agreed form of presentation.

A further point is that not all survivors have a good functional result and in making a comparison of valve replacements one has to consider additional features like diastolic murmurs, regurgitation, and valve failure.

Diastolic murmurs have been a major feature following homograft replacement having been heard in about 46% of my own cases (fig. 8). A much smaller proportion (5.6%) of these are associated with clinical evidence of aortic regurgitation, and the murmurs simply represent technical malpositioning,

Incidence of early diastolic murmurs rises to a maximum at about 1 year and flattens out. Murmurs developing after this time represent valve degeneration.

Degenerative valve failure related to time and type of valve preparation. Note that calcification has its maximum incidence around 4-5 years.
particularly in the early stage of developing the technic, and are not usually progressive.

However, the onset of a late diastolic murmur has a special significance and indicates degenerative changes and frequently the onset of calcification. However, this late diastolic murmur constitutes a useful and early warning of impending failure extending over months or years. This feature is not usually present in mechanical prostheses which when they fail often do so suddenly and catastrophically.

Valve failure in my view means a valve which has had to be removed, and on this basis a total of 46 of the 282 valves inserted by me have failed during the 8-year period under observation, giving an overall failure rate of 16.3% or an average of 2% per year. Of the 46 reoperated patients, 30 are still alive.

Of the causes of failure, avulsion and rupture of the valves usually occurred during the first 18 months of surgery whereas calcification in the freeze-dried valves has been an increasing phenomenon after 3 years (fig. 9). Bacterial endocarditis on the other hand has occurred at any time after valve replacement with an overall incidence of 3.9%.

There has been a dramatic reduction in the number of valve failures, and 42 of the 46 valve failures observed in this long-term study occurred in the first 4 years (fig. 10). Only four valve failures have been noted in the past 4 years. It is tempting to think that this is a result of changing from freeze-dried valves, and reports from other centers using homografts substantiate this view and offer the prospect of even better long-term function.

As in other centers, the incidence of valve failure in the early freeze-dried valve has induced us to follow the trend and use fresh valves stored in antibiotics. Although the indications are that valve failure is markedly reduced, it is too early in their assessment to cry “Eureka,” and we have to be wary since calcific degeneration does not generally become manifest for 2–4 years.

Apart from valve failure, 35 patients have died during the follow-up making a 12.4% late mortality over the 8-year period and with the cause of death in about half of these relating to the valve while the other half were related to the myocardium, that is a 6% total incidence of late deaths related to the valve or less than 1% per year.

On the more positive side of the homograft picture, embolism and anticoagulant problems have been virtually absent from the start with only one doubtful incident, and this contrasts sharply with the continuing evidence of embolism from all mechanical prostheses as illustrated on histograms of reported figures collected from reputable centers over a comparable period of time (fig. 11).

Figure 10
The dramatic reduction in valve failures since 1967 may be related to a change from freeze-dried valves.
Summarizing my view on homografts, I believe we can make the not too sweeping assertion that they have certainly eliminated the threat of embolism and the dangers of anticoagulants, and this is the most compelling argument in favor of their continued use. Although on the present evidence we have not convincingly overcome the danger of late degeneration, I am encouraged by the low incidence of valve-related late deaths and the virtual absence of valve failure in the last 4 years. I believe this augurs well for the future and should result in a more stable homograft survival curve.

I have in the past been gently chided for being unduly critical of the homograft valve, and I hope such reservations as I have mentioned will not be construed as further strictures on the recently reported excellent results with fresh homografts coming from many centers. In fact my enthusiasm for homografts remains undiminished.

To digress to more speculative and controversial topics in relation to valve replacement, one has to take into account the fact that the human valves flex approximately 40 million times a year. On this basis it is inconceivable that any inert nonliving structure (mechanical or biologic) can continue to work indefinitely in this way when lacking the essential and unique feature of the living cell, namely its ability to replace and make good the effects of wear and tear. The mechanical and functional burden imposed on such a valve is analogous to immersing it for at least 10 years beneath the sea and expecting it to function faultlessly in this biologically active medium teeming with scavenging macrophages and in a chemically corrosive electrolyte solution. In fact, it is to the credit of all valves currently being used that they very largely achieve this impossible role.

To anticipate the possibility of late failure and disintegration of our present generation of valves and because of the absence of convincing evidence of cell repopulation in homografts, it has been my practice for the past 4½ years to substitute the living autologous pulmonary valve for the aortic valve in the young patient requiring an isolated aortic valve replacement (fig. 12).

This pulmonary valve switching operation I have carried out in 114 patients, and with the passage of time my enthusiasm grows. The operation is used only in cases of isolated aortic valve disease and in patients under 40 years of age where I anticipate and would like to budget for a life expectancy of 30 years or more. The transplanted valve is autologous, living, sterile, structurally unaltered, of perfect design and functioning under almost ideal environmental conditions, since nature in the

Figure 12

Steps in the pulmonary autograft "switch" operation.
course of evolution has developed almost identical valves in the aortic and pulmonary valve sites.

Comparing the performance of these live autologous valves with preserved homografts, they of course combine all their advantages plus, as far as I can see, an absence of degenerative changes and late valve failure (figs. 13, 14).

This virtual absence of degenerative failure is perhaps not surprising in living tissue, and the evidence so far available from two of these valves deliberately removed for technical malseating approximately 1 year after insertion confirms that we have a living valve with an intact structural and cellular content plus endothelial covering and presumably retained viability (fig. 15).

The incidence of diastolic murmurs in these valves as with homografts is still unsatisfactory (fig. 8), although as with the homografts that associated with clinically significant aortic regurgitation is much lower. As I see it, the one drawback of the method is the need to replace a valve in the right ventricular outflow. However no serious complications have arisen from a homograft replacement in this area nor is calcification visible in these in contrast with homograft replacements for right ventricular outflow atresia in young children. Even allowing for late degenerative changes occurring in this low-pressure area over the years, our experience with the largely destructive and well-established respectable operation of pulmonary valvotomy indicates that a dysfunction of the pulmonary valve is not a significant clinical disability over at least 25 years.

However, having embraced the ideal of using viable tissue and particularly autologous living tissue we have more recently come up against serious difficulties in this quest. By changing to the use of living fascia lata removed at the time of operation and fixed on frames as described by Ionescu, we felt that we had achieved a masterly compromise. These we felt combined all the advantages of an easily made-to-measure valve together with the known advantages of the biologic valve, namely a nonobstructive central flow orifice and an absence of thromboembolism.

About 200 of these valves have been inserted in the mitral, aortic, and tricuspid areas. Briefly, although the follow-up is no more than a little over 2 years and not susceptible to long-term analysis, the results indicate a good maintained valve function in the aortic area, a significant number of failures, and increasing regurgitation in the mitral area and dismal results in the tricuspid area (fig. 16). Although the aortic results remain good and the whole concept remains attractive we have stopped using this technic
Figure 15

Photomicrograph of pulmonary valve cusp removed from the aortic area 1 year after insertion showing retained structure and cellularity.

Figure 16

Fate of fascia lata valves over a 2-year follow-up period. Regurgitant murmurs have been progressive in the tricuspid and mitral valves. Half the aortic failures followed infection.
in all areas until we can analyze our failures more fully and digest the results.

Having briefly discussed performance in a selection of biologic valves, brings me to the more difficult subject of prospects for biologic valves. To my mind, this adds up to the problem of developing a satisfactory mitral valve substitute.

It seems to me that almost any valve substitute currently available can be expected to give good results in the aortic areas but they all have disadvantages when transferred to the mitral area. This is certainly true in my hands for preserved aortic valve homografts when used in an inverted position as a mitral valve substitute (fig. 17), for although they have certain advantages inherent in all biologic valves, particularly in relation to thromboembolism, they do not match up to their long-term performance in the aortic area. Although freeze-dried, their earlier degeneration and higher incidence of perforation must surely be of significance, although I concede that results with fresh valves are encouraging.14

As has been already pointed out, the three cusp fascia lata valves have also performed well in the aortic area but are less satisfactory when inverted in the mitral ring, and I believe this to be true also for all types of mechanical prostheses. Since the materials used, whether homograft, fascia, or plastic and metal, are the same in all instances, whether used as an aortic or mitral replacement, the difference in their behavior in the two areas must lie in their unsuitable design or the environmental factors operating in this area.

Figure 17
Results with freeze-dried inverted aortic homografts in the mitral position. Only a small proportion are asymptomatic and without a murmur at 3 years.

Figure 18
The basic design for the aortic and mitral prosthesis is identical. The valve is simply inverted.

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Flow patterns in the left ventricle comparing the frame-mounted homograft and disc valve with the normal mitral flow pattern.

Put in its simplest terms we spent a good deal of time and effort in designing and developing a successful aortic valve substitute. After that we turn it upside down, fix it in the mitral ring where it meets totally different conditions, and are surprised and disappointed that we then have problems (fig. 18). In the first instance the mitral valve orifice is large and the mechanism of its closure is by two unequal cusps. Furthermore the ring is remarkably mobile and the papillary muscles contribute to valve closure and possibly to the functional efficiency of the ventricle itself.

A small centrally occlusive (or rigid three-cusp) mechanism contravenes almost every design feature mentioned, and the resulting abnormal flow pattern in the left ventricle may well be responsible for disappointing results with reduced functional efficiency and abnormal contractility on left ventricular angiography (fig. 19). In addition, the abnormal and turbulent flow may be responsible for the more recent finding of left ventricular endocardial fibrosis around these prostheses.

This thickening has been noted by us whether we use a Starr or rigid frame-mounted homograft or three-cusp fascia lata prosthesis.

Further evidence for the need to change our mitral valve pattern to a more naturally occurring bicuspid one has come from the operative and autopsy observations on living fascial valves inserted in the mitral region. These have failed in a uniform manner in that the anterior leaflet corresponding to the large anterior mitral cusp has been preserved in all
cases while the two posteriorly placed leaflets have retracted or have even fused to reproduce fairly closely the normal mitral configuration. This phenomenon (bicuspidization) seems to have been brought about by the moulding effects of the blood flow on this plastic living tissue and cannot easily be ignored (fig. 20). It may be that the biologic valve’s greatest challenge and its brightest prospect lie in the possibility that it may enable us to reproduce as nearly as possible the naturally occurring mitral valve as a large flexible bicuspid mechanism.

Our earliest attempts to achieve this were with cadaveric mitral homograft valves which on a theoretic basis should work best. Although these initially functioned efficiently they failed as late as 10–11 months (postoperatively) through shearing of their thin avascular nonliving chordae tendinae. Nevertheless, I suspect that with fresh, living, mitral homografts the possibility of success with this valve is not ruled out, although the papillary muscle fixation is often difficult.

More recently we have completed a large series of dissections and exploratory studies aimed at providing a cylindrical bicuspid valve of fascia lata which can be attached to the papillary muscles or to a flexible strut which does not interfere with the mobility of the valve ring. We have inserted a series of 15 of these valves, and 11 are alive over 1 year and are being assessed at present.

If we are to profit fully from our studies of the naturally occurring valves, then we have to accept all of nature’s criteria, and this applies not only to design but equally to the materials we choose (fig. 21). In this respect,

Figure 20

Failed fascial mitral valve. The aortic-related cusp remains flexible and functional. The “posterior” cusps are retracted and tend to fuse across their common commissure.
fascia lata is probably unsuitable in lacking the elastic or visco-locking features of normal cusp tissue while peritoneum, skin, and pericardium have many of these qualities.\textsuperscript{24} Suitably chosen living biologic tissue should be able to provide us with an antithrombogenic permanent fabric to match the exacting mechanical requirements of a heart valve, and parallel progress is being made by my colleagues in our attempts to prolong the viability of stored living tissue\textsuperscript{22} in nutrient media.

To complete the valve picture, one has to consider the pulmonary and tricuspid valves. Here I have little to add to current knowledge except to note that homografts have again proved themselves to be of great value in reconstructive surgery of the right ventricular outflow. We reported the first replacement of this type in 1966\textsuperscript{28} in a case of pulmonary outflow atresia and have used this technic in 22 cases since, both in atresia and severe Fallot with valve-ring stenosis. All of these survivors' valves function with unimpaired efficiency in spite of calcification noted in the aortic tube surrounding the cusps in practically all cases. Continued function has been confirmed both by catheter and angiography in all cases up to 5 years postoperatively, and the technic has been adopted with enthusiasm in many centers, particularly in the brilliant corrective surgery of truncus and transposition with VSD reported by McGoon and Rastelli.\textsuperscript{24, 29}

The tricuspid valve remains a more distant challenge and for most of us is an area to avoid valve replacement if possible. Where it is unavoidable and also in cases of Ebstein's disease I currently use an inverted aortic homograft fixed on a frame, and I believe this to be the best available tricuspid valve substitute. This therefore means that biologic valves have now been adapted to all four valve areas but they have so far gained acceptance chiefly in the aortic and pulmonary sites.

In conclusion, I have tried as far as possible to retain a measure of objectivity in discussing these valves, although this is not an attitude that comes easily when discussing a subject of major interest. It seems at present that the honors are fairly evenly divided between mechanical and biologic valves as far as operative mortality and early performance are concerned. However, I feel satisfied that the continued performance and prospects are ultimately better for the aortic patient with a biologic valve free from the hazards of embolism and sudden mechanical failure.

The more distant prospects are speculative, but I would hope that mitral valve patients should be able to share this outlook without the tyranny of pills, doctors, and electrocardiograms and with a chance to live and function as normal members of the community, even to hope and plan a future, or in Hamlet's immortal words:

\begin{quote}
\ldots \text{“tis a consummation Devoutly to be wish'd. To die, to sleep: To sleep: perchance to dream: ay, there's the rub.”}
\end{quote}

References

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