Long-term follow-up of aortic valvar grafts

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This report deals firstly with the long-term follow-up of aortic valve homografts, and secondly with the current results obtained when valves stored and sterilized in a balanced salt solution (Hanks's) containing selected antibiotics are used.

The long-term data relate to all patients having isolated aortic valve replacement with an aortic homograft valve (Barratt-Boyes, 1965) at Green Lane Hospital from the beginning of this operation in August 1962 over a seven-year period. The follow-up is complete, except for one untraced patient, up to August 1969, and has been by cardiologists only (over 90 per cent of the patients were examined by one cardiologist at Green Lane Hospital). As no other prosthesis was used, all variants of aortic valve disease are included, and, in contrast with other published reports about homograft valves (Malm *et al.*, 1967; McDonald *et al.*, 1968; Stinson *et al.*, 1968; Karp and Kirklin, 1969), the series does not consist of selected patients. Lastly, and of great importance, these long-term results relate almost exclusively to chemically treated homograft valves, a technique of valve preparation abandoned in August 1968. A group of 13 patients who received fresh untreated valves early in the series is too small to affect the overall follow-up, and the current technique of antibiotic sterilization is too recent to have long-term significance.

Mortality

The hospital mortality in the 564 patients was 8.8 per cent, and was higher for aortic stenosis at 10.9 per cent than for aortic incompetence at 6.2 per cent.

The late mortality was 13.5 per cent of all patients operated upon (Table 1). Approximately 9 per cent of patients died from causes other than valve failure and will not be discussed further. Homograft valve failure was the cause of late death in 4.6 per cent of all patients operated upon, and in these death was the result of homograft valve incompetence in every instance - peripheral leak around the graft, malplacement with central leak, cusp

rupture, or endocarditis. Thromboembolism has not occurred and anticoagulants have not been used. Homograft stenosis from leaflet calcification has been rare and not a cause of late death.

More significant data are obtained by relating the mortality to the year operation was performed (Fig. 1). This graph gives in percentages the hospital mortality, the late mortality from causes other than valve failure, and the late mortality from valve failure. Thus, for the 45 patients operated upon in 1962 and 1963 combined, there was a 4.4 per cent hospital mortality. In the subsequent 6 to 7 years of follow-up, 20 per cent have died from factors other than valve failure and a further 11 per cent from valve failure. Expressed differently, 65 per cent are alive after 6 to 7 years. After 5 years 60 per cent are alive, and for 4, 3 and 2 years of follow-up the figure is approximately 80 per cent.

Fig. 1 also includes an additional 37 patients with valve failure who remain alive after re-operation, and when these patients are combined with those who died from valve failure the total incidence of valve failure for each year of operation is obtained. This total valve failure rate is examined in more detail in Fig. 2. Valve failure has occurred in 69 patients, or 12.2 per cent of all those operated upon. In patients operated upon in 1962-63, valve failure has subsequently occurred in 26 per cent; and for 1964 in 28 per cent. For the years 1965 to 1968 the total valve failure rate has varied between 7 and 11 and averages 9 per cent. Deaths from valve failure in these later years have varied between 2 per cent and 4 per cent.

Causes of homograft failures

The causes of homograft valve failure are:

- a) Late stenosis from leaflet calcification. This has occurred in 2 patients (0.4%), both successfully reoperated upon 4 years post-operatively.
- b) Late endocarditis has occurred in 12 patients (2.1%) and has been slightly more

TABLE 1 *Aortic valve homografts (August 1962–August 1969): isolated aortic replacement in 564 patients. Causes of late death*

Coronary atheroma	13			
Myocardial Sudden	14	(3)*	36	6.4%
	9	(3)		
Unrelated to valve	11			
Uncertain	3	(3)	14	2.5%
Valve failure				
Peripheral leak	6	(1)		
Malplacement	2			
Cusp rupture	10	(1)	26	4.6%
Endocarditis	8			
Total			76	13.5%

* No necropsy.

common in patients followed for the longest time (Fig. 2).

c) A peripheral suture line leak sufficient to cause death or require reoperation has occurred in 3.2 per cent of all patients operated upon (included in this group are 3 patients with severe central incompetence due to valve malplacement). This is a purely technical matter and has been of little consequence (1% to 3%) since the introduction in December 1964 of a technique to reduce the diameter of the host aortic root when it proved too large for the available homograft valve (aortic root tailoring) (Barratt-Boyes and Roche, 1969). Less major peripheral leaks, which in earlier years were an important cause of incompetent murmurs, have become uncommon from 1967 onwards with the addition of vertical mattress sutures (Barratt-Boyes and Roche, 1969) which abolish most of the dead space between the homograft valve and the host aortic root. Our experience indicates that incompetence due to a peripheral suture line leak is apparent and stable within 3 months of operation (Brandt *et al.*, 1969).

d) Cusp rupture was verified as a cause of important late incompetence, causing death or requiring reoperation in 37 patients (7.2%) at the time of review in August 1969, and is clearly the most important complication of homograft valves.

The incidence of rupture was related to the method of valve preparation (Table 2). While there is no statistically significant difference in the incidence with chemical sterilization (using beta propiolactone or ethylene oxide gas) and storage either by freeze-drying or in Hanks's solution, it is significant that rupture has not been recognized in any of the 13 sterile untreated valves, all of which have been followed now from 5 to 7 years. Its absence

FIG. 1 The combined hospital and late mortality is indicated by the heavy continuous line and the percentages above this line ('other valve failure') are patients alive after reoperation for valve failure. The total valve failure rate is represented by the diagonally hatched section; this portion of the graph is examined in further detail in Fig. 2.

FIG. 2 This graph analyses all proved cases of valve failure. It includes 6 more patients than are listed in this category in Fig. 1 because these 6 patients survived reoperation only to die later from other causes. They are thus included in the 'late deaths other' category of Fig. 1.

with the current technique of antibiotic sterilization was less significant when this review was made, although the follow-up in this group now extends almost to 2 years.

The time of presumed onset of rupture after operation in 35 of these proved cases is shown in Fig. 3. This event was signalled either by the sudden onset of an aortic diastolic murmur or, if such a murmur was already present when the patient left hospital, by a sudden increase in the degree of aortic incompetence. Most ruptures have occurred in the first 2 years, as only 7 valves have been known to rupture after this period out of 300 at risk beyond 2 years and 160 at 4 years. It is probably significant also that, while all the ruptured valves were chemically sterilized, those stored wet in Hanks's solution have not been known to rupture after 18 months (Fig. 3), though 135 such valves have been followed from 2 to 4 years. Rupture after 2 years seems to be more common, therefore, in freeze-dried valves. In the 7 freeze-dried valves that ruptured after 2 years, leaflet calcification was present in 4.

The true incidence of cusp rupture is probably higher than the proved incidence of 7.2 per cent, for the incompetence produced by rupture, though of sudden onset, usually increases slowly and has never been a cause of sudden death. The delay between the presumed onset of cusp rupture and reoperation has varied from 1 to 34 months and has averaged 8½ months. It seems likely that any change in valve competency occurring 3 months or more postoperatively is almost always due to cusp rupture.

Survival rates

The final histogram (Fig. 4) shows the percentage survival for each year of operation with each method of valve preparation. Hospital mortality has been excluded, as it bears no relation to this factor. For freeze-dried valves (most of which were sterilized with beta propiolactone, though 20 were collected sterile) the figures show 60 per cent alive at 6 to 7 years, 70 per cent at 5 years, and 87 per cent at 4 years. For Hanks's solution chemically sterilized valves the figures are 43 per cent at 5 years (with only 14 patients at risk), and 94 per cent at 4 years. There is probably no significant difference in survival between these two groups. By contrast, 85 per cent of the 13 patients with fresh untreated valves collected sterile were alive after 6 to 7 years; in fact, no patient in this group has died from valve failure. The survival for the current antibiotic form of sterilization was 100 per cent at the time of this review in August 1969,

TABLE 2 *Aortic valve homografts (August 1962–August 1969): cusp rupture in patients leaving hospital*

Valve preparation		Number of valves	Number of ruptures	Percentage incidence
Sterilization	Storage			
Beta propiolactone	Freeze-drying	201	22	10.9
Beta propiolactone	Hanks's	202	12	5.9
Ethylene oxide	Hanks's	43	3	7.0
Untreated*	Hanks's	13	0	0
Antibiotics	Hanks's	55	0	0
Totals		514	37	7.2

*Collected sterile.

but the follow-up was then limited and this material is analysed further in the final section.

Summary of late results

The data show that the one remaining important cause of late valve failure with a chemically treated homograft valve is leaflet rupture. Endocarditis is uncommon, and the incidence of major incompetence from technical factors (peripheral and central leak) has been acceptably low over the past 5 years. Homograft valve stenosis from leaflet calcification is also unimportant up to 7 years after insertion (Barratt-Boyes *et al.*, 1969). The best results were achieved with untreated valves which

FIG. 3 *An analysis of the presumed time after operation of the onset of cusp rupture, each patient being represented by a circle or a cross.*

FIG. 4 Percentage survival relative to the method of valve preparation with the figures above each column indicating the number of patients at risk. As these figures indicate, the valves were initially collected sterile and stored for short periods in Hanks's solution, but this was soon replaced by freeze-drying to allow longer storage. All but 20 of these freeze-dried valves were beta propiolactone (BPL) sterilized. From 1964 onwards some BPL valves were stored in Hanks's solution, and during 1966-67 80 per cent of the valves used had been stored in this way (for a maximum period of 6 weeks). In the latter part of 1967 ethylene oxide gas (EO) replaced BPL for an 11-month period but was then abandoned in favour of the current technique of antibiotic sterilization.

FIG. 5 A section from the middle third of an aortic homograft leaflet 5 years after insertion. This valve was used 5 days after sterile collection. The leaflet is approximately twice normal thickness, the increase being due to a broad layer of newly formed cellular connective tissue on the upper (aortic) aspect of the leaflet. The darkly staining band near the centre is a deposit of acid mucopolysaccharides. Although not visible with this magnification, the entire leaflet contains many fibroblasts. (Colloidal iron. $\times 30$.)

FIG. 6 A higher power view of the aortic aspect of the cusp showing many fibroblasts and young collagen fibres. (H. and E. $\times 100$.)

FIG. 7 Surgical specimen of aortic homograft valve 9 months after insertion. This valve had been sterilized and stored by immersion in antibiotic Hanks's solution for 22 days before use. The leaflets were normally pliable but showed whitish thickening near the base due to organizing fibrin deposits.

had been collected sterile, stored in Hanks's solution, and inserted within 1 to 3 weeks. Thus in this group there was an 85 per cent survival after 5 to 7 years; no patient died from valve failure; leaflet rupture did not occur; and leaflet calcification was not recognized.

The excellent results achieved with the fresh untreated homograft correlate with the histological findings in the leaflet tissue. Specimens of the untreated type of valve at 5 years have shown preservation of collagenous and elastic tissue, an excess amount of acid mucopolysaccharide ground substance, and more than the normal number of fibroblasts (Fig. 5 and 6). In contrast, chemically treated leaflets have never become covered or incorporated by host tissue and have remained acellular (Smith, 1967). They appear to undergo a slow progressive degeneration and show a tendency towards late calcification. Histological study of our human material leads us to believe that the favourable host reaction to the untreated valve occurs because the ground substance of the leaflet is undamaged rather than because the grafted fibroblasts survive.

Current technique of homograft valve preparation

The data indicate that a fresh untreated homograft valve is the ideal preparation, but unfortunately the logistics make this an impractical solution, at least in a large clinic. As an

alternative we have used a technique of storage and sterilization in an antibiotic Hanks's solution (Table 3) in the belief that this technique does not damage the ground substance of the leaflet and will allow a similar host reaction to that which occurs with the untreated

TABLE 3 Homograft valves: antibiotic sterilizing solution

Penicillin	50 units/ml.
Streptomycin	1 mg./ml.
Kanamycin	1 mg./ml.
Amphotericin B	25 units/ml.

leaflet. With this method the valve has been collected from routine necropsy material as cleanly as possible and stored in the solution at 4°C. If cultures are negative at 14 days, and approximately 90 per cent of valves have been sterile within this interval, the valve is cleared for use. One-third of these valves have been used within 14–28 days of collection and

FIG. 8 A section from the junction of mid distal thirds of the leaflet opened out in Fig. 7, showing the organizing fibrin deposit on the upper aortic aspect. The darkly staining tissue within the leaflet is newly formed acid mucopolysaccharide material laid down preparatory to new collagen formation. Occasional fibroblasts are present in this portion and more numerous fibroblasts in the proximal or basal third of the leaflet. (Colloidal iron $\times 30$.)

four-fifths within 60 days. Valves stored longer than 60 days have been used mainly in elderly patients.

Results with antibiotic sterilized aortic homograft valves

From September 1968 to April 1970 135 patients have had isolated aortic valve replacement with an antibiotic-treated homograft valve. There were 8 hospital deaths (5.9%) and 4 late deaths, all of which came to necropsy. None were due to valve failure.

On subsequent review no patient has developed an aortic incompetent murmur for the first time 3 months or more after operation, and no patient, therefore, has shown the clinical features of cusp rupture. At the time of their last examination, 91 of the 127 patients leaving hospital (72%) had no aortic diastolic murmur. Of the 36 with a murmur, 30 were considered to have trivial incompetence and 4 mild unimportant incompetence. One patient with an associated sinus of Valsalva aneurysm had moderate but well-tolerated incompetence, and one had developed severe incompetence. This 67-year-old-man is the only patient to show progressive postoperative incompetence in the group to date. He came to reoperation at 9 months and was found to have central incompetence from recurrent dilatation of a medionecrotic aortic root. The homograft valve leaflets were intact (Fig. 7) and histological study showed changes similar to those found in the sterile fresh untreated valves (Fig. 8 and 9).

These results with antibiotic treated homograft valves are greatly superior to any we have obtained with chemical methods of sterilization, and, though the follow-up remains relatively short, they are considered likely to be significant.

Patients in this series have been operated upon by staff surgeons and senior residents in training at the Cardiothoracic Surgical Unit, Green Lane Hospital. The follow-up data were largely collected by Dr. A. H. G. Roche and the histology was provided by Dr. G. Hitchcock.

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FIG. 9 Higher power view taken from the distal edge of the organizing fibrin deposit shown in Fig. 8. Fibroblastic nuclei are seen in this material but are absent from the substance of the leaflet. (H. and E. $\times 100$.)

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