Aortic Homograft Valve Replacement

A Long-Term Follow-Up of an Initial Series of 101 Patients

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SUMMARY

An initial series of 101 patients with a homograft aortic valve has been reviewed from 4 to 6 years postoperatively. There were six hospital and 24 late deaths, eight of which were due to homograft valve failure. The 71 surviving patients were all symptomatically improved. Anticoagulants were not used, and emboli were thought not to originate from the valve.

Important incompetence occurred in 27 patients and reoperation was undertaken in 17 of these. The causes were peripheral leaking of the suture line, cusp rupture, bacterial endocarditis, and valve misplacement.

Leaflet calcification produced stenosis, requiring reoperation in two patients, and was significant in eight other valves. Precipitating causes, present in eight of the 10 cases, were imperfections in the original homograft, valve misplacement, or endocarditis.

Both cusp rupture and leaflet calcification were related to the method of valve preparation as neither was encountered in untreated valves. For this reason, chemical sterilization and freeze drying have been replaced by sterilization and storage in an antibiotic Hank's solution.

Additional Indexing Words:
Homograft valve calcification  Homograft leaflet rupture  Myocardial disease
Homograft aortic valve incompetence  Homograft aortic valve stenosis
Cardiothoracic ratio  Valve preparation

In view of the poor prognosis for patients with severe aortic valve disease and the low hospital mortality following aortic valve replacement, it is reasonable to proceed with operation in such patients. In this hospital the aortic homograft valve has been used for aortic valve replacement, and serial review has indicated that in the majority of patients this valve functions satisfactorily and affords relief of symptoms. The first 101 patients operated upon during the first 2 years from the inception of this technic in August 1962 have now been followed from 50 to 74 months, and the results of this relatively long-term follow-up are presented here in detail. This same group of patients was assessed 4 to 28 months postoperatively in an earlier report.

Clinical Material

Forty-two patients presented with dominant or pure aortic incompetence, 48 with dominant or pure calcific aortic stenosis, and 11 with both aortic and mitral valve disease which required surgical correction (10 in this category had aortic incompetence and one had stenosis).

The symptomatic state and hospital morbidity, together with the cause of the six hospital deaths in these 101 patients, have been presented in the previous report and are not, therefore, detailed here. Much of this information is given in later tables, where age, symptoms, cardiothoracic ratio, and electrocardiographic findings are related to early and late mortality.
The surgical technic used was described in 1964 and did not include either aortic root tailoring or vertical mattress sutures to obliterate most of the dead space between graft and host, both of these latter technics having been introduced later to lower the incidence of homograft valve incompetence.

Sixteen of the homograft valves were collected under sterile precautions and stored in Hank's solution containing 5,000 units of penicillin and 0.2 ml of 5% streptomycin sulfate, hereafter often referred to as "untreated valves," and a further 23, also taken under sterile conditions, were freeze dried. Eight homografts were sterilized with 1% beta propiolactone and stored in Hank's solution and 54, also sterilized in this way, were freeze dried.

**Late Mortality**

Seventy-one patients were alive at the time of review and 66 were examined by one of us (A.H.G.R.). For the remaining five, adequate clinical data were available from cardiologists in other centers. Of the 24 late deaths, 13 occurred in patients with preoperative aortic incompetence (31%), 10 in patients with stenosis (21%), and one in the multivalve group (10%). Eighteen either died in this unit or were seen shortly before death, and six died elsewhere without being recently seen by us, adequate data being available in five of these. When it has been brought to our attention that the cardiac status of a patient changed subsequent to review here, the data have been altered accordingly, to November 1, 1968.

The cause of late death was established by necropsy in 22 of the 24 patients and is related to the time after operation in table 1. Reoperation for homograft valve incompetence had been undertaken in seven of these patients (table 1), a second homograft valve being inserted.

**Homograft Valve Incompetence**

This has been regarded as the major cause of death in the eight patients regardless of associated causes of death, namely coronary artery atheroma (present in two), moderate residual mitral incompetence (present in one), or complete heart block (present in one). The valve incompetence was graded as moderate or severe in these cases. Four of these patients died in hospital following a second operation. The incompetence was due to a peripheral leak in the suture line in three patients; in the remaining five the leak was central and due to cusp rupture in three, malpositioned valve in one, and endocarditis in one.

**Coronary Artery Atheroma**

These five patients were aged 51, 60, 62, 67, and 72 at the time of death, which was relatively sudden in all instances. The youngest was a diabetic, and another dying 4 months following operation had had a probable infarct 2 months preoperatively. One had severe coarctation of the aorta, a congenital mitral valve deformity with some stenosis, and intermittent complete heart block, before operation and at the time of death.

**Cardiomyopathy**

Myocardial disease with congestive heart failure and cardiomegaly was the cause of death in six patients, aged 22, 29, 30, 53, 55,
and 59 at the time of death, which occurred from 11 to 71 months after operation. The original valve lesion was incompetence in four and stenosis in two. Mild mitral valve disease contributed in one and essential hypertension in another, but in the remaining four there was no apparent reason for the onset of congestive heart failure and progressive cardiomegaly within months of operation. Necropsy was not performed in one case, but in the remainder the left ventricle was grossly hypertrophied with interstitial fibrosis. Moderate coronary artery atheroma was present in one and significant narrowing of the small coronary arteries by intimal fibrosis in three.

Sudden Death

Sudden unexpected death, presumably from arrhythmia, occurred in two asymptomatic patients, 4 and 5 months after operation. While no obvious cause of death was found at necropsy, the left ventricle in both showed marked interstitial fibrosis and widespread narrowing of the small coronary arteries without significant proximal atheroma.

Unrelated Cause

Death unrelated to the heart occurred from disseminated carcinoma of the prostate at 24 months in one patient and from a stroke at 34 months in another. The latter patient had undergone carotid endarterectomy shortly before death.

Cause Uncertain

The cause of death is uncertain in one patient, dying overseas without autopsy 51 months after operation. This patient had a successful reoperation for recurrent incompetence 26 months prior to death. The likely cause was hypertensive heart failure.

In summary (table 1), late death from valve failure occurred in eight patients (8.4% of those leaving hospital) and myocardial factors (coronary atheroma, cardiomyopathy, and arrhythmia) were responsible for all but three of the remainder (14%).

The majority (17) of the late deaths occurred in the first 3 years, although deaths from valve failure were equally distributed between the first and second 3-year periods (table 1).

Table 2

<table>
<thead>
<tr>
<th>Mortality Relative to Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Absent</td>
</tr>
<tr>
<td>Effort dyspnea only</td>
</tr>
<tr>
<td>Angina or syncope</td>
</tr>
<tr>
<td>Heart failure or angina decubitus</td>
</tr>
<tr>
<td>Totals</td>
</tr>
</tbody>
</table>

* Includes deaths due to coronary atheroma, cardiomyopathy, and arrhythmias (see tables 3, 4, and 5).

Table 3

<table>
<thead>
<tr>
<th>Mortality Relative to Cardiotoracic Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiotoracic ratio (%)</td>
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<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>55 or less</td>
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<tr>
<td>56 to 60</td>
</tr>
<tr>
<td>61 to 75</td>
</tr>
<tr>
<td>Totals</td>
</tr>
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Table 4

Mortality Relative to Electrocardiogram Changes

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<th>Mean frontal axis</th>
<th>Number of patients</th>
<th>Mortality</th>
<th>Late</th>
<th>Other</th>
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<td>Hospital</td>
<td>Myocardial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left axis deviation</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>(axis less than $-30^\circ$)</td>
<td>16</td>
<td>0</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>$0^\circ$ to $-30^\circ$</td>
<td>40</td>
<td>0</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Normal</td>
<td>45</td>
<td>6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Intraventricular conduction</td>
<td>Complete bundle</td>
<td>6</td>
<td>0</td>
<td>2</td>
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<tr>
<td></td>
<td>branch block</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>95</td>
<td>6</td>
<td>11</td>
<td>11</td>
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</tbody>
</table>

Table 5

Mortality Relative to Age at Operation

<table>
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<tr>
<th>Age (yr)</th>
<th>Valve lesion</th>
<th>Aortic incompetence</th>
<th>Aortic stenosis</th>
<th>Multivalve</th>
<th>Total patients</th>
<th>Mortality</th>
<th>Late</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hospital</td>
<td>Myocardial</td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>10-19</td>
<td>5</td>
<td>0</td>
<td>0</td>
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<td>20-29</td>
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<td>0</td>
<td>3</td>
<td>0</td>
<td>11</td>
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<td>30-39</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>6</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>50-56</td>
<td>10</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>60-69</td>
<td>6</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Totals</td>
<td>42</td>
<td>48</td>
<td>11</td>
<td>0</td>
<td>101</td>
<td>6</td>
<td>13</td>
<td>11</td>
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</tbody>
</table>

The influence of the patient's symptoms, degree of cardiac enlargement, certain electrocardiographic changes, and age on mortality are examined in tables 2 to 5. The 13 late deaths from myocardial factors are of chief importance in this analysis, as deaths from other causes would be expected to have a random distribution. The data indicate that late mortality from myocardial factors was probably significantly greater in patients with a cardiothoracic ratio above 60% ($P = 0.05$) and highly significant when there was a left axis deviation ($P = 0.0005$). There was no significant correlation with a preexistent complete bundle-branch block, the preoperative symptomatic state, or age.

Late Morbidity

Homograft Valve Incompetence

Adequate clinical data were available for assessment of homograft aortic valve incompetence in all 95 hospital survivors and, in addition, aortography was performed in 27, in most instances as part of a routine follow-up study. When there was a discrepancy between the clinical and angiographic methods of grading, the angiographic classification was used. In the 17 patients who underwent reoperation for incompetence, the first operative result only was assessed and when late death occurred the degree of incompetence was that existing prior to death.

The degree of homograft incompetence is shown in table 6. Trivial incompetence was not considered hemodynamically significant and was not associated with any alteration in the character of the pulse or the pulse pressure. Such incompetence has been classified with that of patients without any early diastolic murmur as "no significant incompetence." Mild incompetence was associated with minor alteration in the character of the pulse, but the pulse pressure remained less than half the systolic blood pressure.
AORTIC HOMOGRAFT VALVE REPLACEMENT

Table 6

<table>
<thead>
<tr>
<th>Degree of incompetence</th>
<th>Original valve lesion</th>
<th>Totals</th>
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<tbody>
<tr>
<td>None</td>
<td>Incompetence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stenosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multivalve</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Trivial</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Mild</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Totals</td>
<td>41</td>
<td>45</td>
</tr>
</tbody>
</table>

ate and severe incompetence were of hemo
dynamic significance and have been grouped
together as “important incompetence.”

Fifty-nine patients were found to have a
good result with no significant aortic incompe-
tence. The incidence of good results was
higher in patients presenting preoperatively
with aortic stenosis, where 32 of 48 obtained
good results, compared to 21 of 41 patients
presenting preoperatively with aortic incompe-
tence and six of 11 patients undergoing
multivalve procedures.

Six of the nine patients with mild incompe-
tence were asymptomatic and three had
symptoms unrelated to the valve.

Important incompetence was present in 27
patients. As previously noted, eight died from
this cause and reoperation was undertaken
because of the incompetence in 17 of the 27.
The cause of incompetence has been estab-
lished in 21 of these 27 patients. Rupture of
one or more of the homograft valve cusps had
occurred in nine (eight of these in freeze-
dried valves), a peripheral leak in the suture
line in seven, bacteriologically proven late
bacterial endocarditis in two, probably endo-
carditis in one, and prolapse of a cusp from
imperfect valve placement in two. The inci-
dence of important homograft valve incom-
peience was greater in those presenting with
aortic incompetence (14 of 42) than in those
presenting with aortic stenosis (10 of 48).
Important incompetence due to a peripheral
leak in the suture line was found only in those
originally presenting with aortic incompe-
tence.

Patients with absent, trivial, or mild homo-
graft incompetence at the time of hospital
discharge, have had no significant progression
in the degree of incompetence on subsequent
follow-up, unless cusp rupture or bacterial
endocarditis supervened.

Stenosis and Calcification

Stenosis

Two patients required reoperation for cal-
cific stenosis of the homograft leaflets at 46
and 48 months after operation; both had
presented with calcific aortic stenosis. In one,
the homograft valve was atheromatous and
showed early leaflet calcification at the hinge
area when inserted and obviously should not
have been used. In the second patient, the
valve was recognized to be too large at the
time of insertion and, although there was no
gradient initially, the valve leaflets were
redundant, folded, and therefore unable to
function normally. Severe stenosis has not
been suspected clinically in any other patient.

In 24 patients cardiac catheterization was
undertaken from 31 to 61 months following
surgery, in most of them as part of a routine
follow-up study. Apart from the two patients
requiring reoperation for stenosis, peak gra-
dients in the systolic pressure during rest
between the left ventricle and ascending aorta
greater than 20 mm Hg (ranging from 21 to
42 mm) were found in only six, and clinically
significant stenosis had not developed in any.
Fourteen of these patients had been cathe-
terized previously, 12 to 24 months after
operation. Comparison of the pressure gradi-
ents showed an increase over the 2 to 4-year
interval of 10 mm Hg or less in 10 patients, of
approximately 20 mm Hg in three, and of
60 mm Hg in one. When cardiac output
measurements were taken into account, this
change in gradient was of doubtful signifi-
cance except in the patient with the 60
mm Hg rise, when reoperation revealed
calcific stenosis of the leaflets.

Cinefilm Screening for Calcification

Thirty-six patients were screened for calcifi-
cation (table 7). A 6-inch intensifier was used
and cinefilm recordings made either in the
lateral projection at the time that an aortogram was performed (16) or in three separate projections (20).

In four patients no calcification could be seen in the aortic root region. Scattered flecks of calcification were seen in the aortic wall of the remaining 32, but in only one (one of the two patients requiring reoperation for stenosis) was calcification considered to be in cusp tissue because of the relative movement between cusps and aortic ring. The extent of calcification was limited to sparsely scattered flecks, which were not visible using a 9-inch intensifier (grade 1) in 14 patients. More numerous flecks of calcification of mild to moderate extent (grade 2) were seen in 12, and more extensive calcification, usually involving the entire circumference of the aortic ring (grade 3) in six, this including the two requiring reoperation for homograft stenosis, but in all instances the calcification was considerably less than that seen in patients presenting with calcific aortic stenosis.

In the group with preoperative aortic incompetence (table 7) late calcification may be more significant than in patients with calcific aortic stenosis, where some calcium was usually left behind in the valve bed, for it was not possible to differentiate between calcification in the homograft aortic remnant and host aortic root. Analysis of the four patients with preoperative incompetence and grades 2 or 3 aortic wall calcification indicated, however, that three had heavy calcification of the aortic root preoperatively (in two this was syphilitic in origin) and the other had late bacterial endocarditis which had presumably produced the calcification.

**Gross and Microscopic Calcification**

Valves obtained at autopsy or reoperation less than 3 years after insertion rarely showed calcification, and when present it was never significant. After 3 years, however, calcification was visible to the naked eye in both the aortic remnant of the graft and the leaflets in 12 of the 18 specimens. A detailed description of these valves follows.

Aortic wall calcification was evident microscopically in every case but was trivial in six of the 18 where the deposits were confined to tissue compressed by sutures at the upper or lower margins of the graft. In nine cases calcification, while never bulky, involved the whole graft annulus in circumferential fashion with scattered or confluent foci in other parts of the aortic remnant. In the remaining three, calcification was intermediate in extent.

Leaflet tissue calcification was absent in five specimens (36, 37, 40, 40, and 60 months postoperatively) and trivial in three (36, 47, and 70 months postoperatively). In these three it presented as an isolated deposit in acellular graft collagen in the right cusp not visible macroscopically in one specimen, and as a single tiny vegetation in the other two. Significant leaflet calcification was noted in the remaining 10 specimens. It was of a mild degree and not sufficient to interfere with leaflet function in five (fig. 1) and moderate to severe in five (44, 46, 47, 48, and 56 months postoperatively). In two of these five specimens the calcification had produced valve stenosis, and in three it was associated with dominant incompetence. Precipitating causes were present in eight of the 10 valves with significant calcification, namely, imperfections in two of the grafts when they were inserted (early leaflet calcification and a bicuspid homograft); one valve was too large and the leaflets were folded and redundant; in three

### Table 7

**Postoperative Cinefilm Screening for Valve Calcification (6-Inch Intensifier)**

<table>
<thead>
<tr>
<th>Preoperative lesion</th>
<th>No. of patients</th>
<th>Absent</th>
<th>Calcification</th>
<th>Homograft</th>
<th>Aortic wall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Incompetence</td>
<td>14</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Calcific stenosis</td>
<td>22</td>
<td>1</td>
<td>7</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>36</td>
<td>4</td>
<td>14</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

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there was major associated peripheral-space filling and leak with resultant leaflet distortion; and in two, proven endocarditis. It is perhaps significant that all five valves with moderate to severe leaflet calcification came from patients who presented initially with heavy aortic root and leaflet calcification.

There was no clear correlation between the degree of leaflet calcification and the method of valve preparation. However, the two untreated valves available for examination 40 and 60 months after operation were free of calcification (table 8). Moreover, although eight of the 10 valves with significant calcification had been freeze dried, five of the eight with absent or trivial calcification were also freeze dried, including the specimen examined at 70 months.

In summary, it would appear that calcification invariably occurred in the aortic wall remnant of the graft after 3 years, but was confined to tissue compressed by sutures in one third of the specimens and was apparent macroscopically in only two thirds. It was not a cause of outflow obstruction. Leaflet calcification was significant in 10 of 18 specimens. It was a cause of stenosis, however, in only two patients. In five of the 10 specimens exhibiting leaflet calcification, the deposits were small and in eight (including the two with stenosis) precipitating factors were present. It was of interest that both the untreated valves examined after 3 years were free of leaflet calcification.

**Complete Heart Block**

Permanent complete heart block, not present preoperatively, occurred in two patients, although in one it did not appear until 6 months after operation. Implantable pacemakers were inserted into both; one remains
Table 8

State of Untreated Aortic Homograft Values

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at operation (yr)</th>
<th>Diagnosis</th>
<th>Time of review postop. (mo)</th>
<th>Duration storage (days)</th>
<th>Complications during follow-up</th>
<th>Aortic root calcification (cine study)</th>
<th>Incompetence</th>
<th>Systolic pressure gradient (mm Hg) left ventricle/aorta</th>
<th>Cardiac symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>AI</td>
<td>4</td>
<td>?</td>
<td>Infarction (died)</td>
<td>—</td>
<td>Trivial</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>AI</td>
<td>16</td>
<td>24</td>
<td>Cardiomyopathy (died)</td>
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<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>AS/MS</td>
<td>9</td>
<td>3</td>
<td>Peripheral leak (reop.)</td>
<td>—</td>
<td>Severe</td>
<td>—</td>
<td>—</td>
</tr>
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<td>4</td>
<td>17</td>
<td>AI</td>
<td>40</td>
<td>4</td>
<td>Endocarditis (reop.)</td>
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<td>Severe</td>
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<td>—</td>
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<tr>
<td>5</td>
<td>56</td>
<td>AS</td>
<td>60</td>
<td>5</td>
<td>Misplaced valve (reop.) coronary atheroma</td>
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<td>Severe</td>
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<td>4</td>
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<td>AI</td>
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<td>45</td>
<td>AI/MS</td>
<td>56</td>
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<td>Residual mitral valve disease</td>
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<td>0</td>
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</tr>
<tr>
<td>13</td>
<td>43</td>
<td>AI/MS</td>
<td>63</td>
<td>3</td>
<td>Some cardiomegaly</td>
<td>0</td>
<td>None</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>59</td>
<td>AS</td>
<td>64</td>
<td>3</td>
<td>Stroke</td>
<td>2</td>
<td>Mild</td>
<td>0</td>
<td>None</td>
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<tr>
<td>15</td>
<td>36</td>
<td>AI</td>
<td>70</td>
<td>26</td>
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<td>1</td>
<td>Trivial</td>
<td>14</td>
<td>Mild dyspnea</td>
</tr>
<tr>
<td>16</td>
<td>14</td>
<td>AI</td>
<td>74</td>
<td>16</td>
<td>None</td>
<td>—</td>
<td>Trivial</td>
<td>8</td>
<td>None</td>
</tr>
</tbody>
</table>

*Left ventricle/brachial artery.

Abbreviations: AI = aortic incompetence; AS = aortic stenosis; MS = mitral stenosis.
well 5 years after surgery, and the other died at reoperation for homograft incompetence 3 years after surgery.

**Systemic Emboli**

Three patients suffered transient visual loss in the early postoperative period and in one this was associated with aphasia of a few days' duration. These episodes were probably due to platelet emboli from the healing suture line of the valve, as these were seen in the retinal arteries in one patient. Three patients have been thought to have had systemic emboli at a later stage. One patient suddenly developed pain in the left side of the body 2 months after operation, at a time when his heart reverted from atrial fibrillation to sinus rhythm, and he has residual hemi-anesthesia; one patient suffered transient obscuration of vision associated with bacterial endocarditis 5 years after surgery, and one multivalve patient with a Starr-Edwards mitral valve prosthesis had an episode of ataxia lasting several days, with complete recovery. Possible systemic embolism has occurred in four others. This presented as transient visual loss in two older patients, one with associated mitral valve disease and atrial fibrillation and as a stroke in two patients, both with known cerebrovascular disease and severe widespread arteriosclerosis. Anticoagulants were not used postoperatively, except in the four multivalve patients with a Starr-Edwards mitral prosthesis.

**Symptomatic Result (Fig. 2)**

At the time of review all 71 surviving patients were symptomatically improved. Forty-three were symptom free or suffered from mild effort dyspnea only and did not have important incompetence of the homograft valve. Forty of these showed a convincing reduction in heart size and in 31 the cardiothoracic ratio was less than 55%.

Significant symptoms not related to dysfunction of the homograft valve were present in 10. In six, symptoms were secondary to coronary atheroma, in three to mitral valve disease, and in one to asthma.

Five patients with moderate or severe aortic incompetence were asymptomatic, and four of these were actively employed, while one patient with moderate aortic incompetence had moderate effort breathlessness but was improved by her operation.

Twelve patients were alive following reoperation, which in three was too recent to assess the result. In seven a good result was achieved and in two minor symptoms only were present, but incompetence had recurred.

**Result with Untreated Valves**

As particular interest attaches to the valves which were collected sterile and stored for 1 to 26 days in Hank's solution, the outcome in the 16 patients receiving these valves has been summarized in table 8.

Two patients died 4 and 16 months postoperatively from myocardial factors with good valve function, and three underwent successful reoperation at 9, 40, and 60 months because of valve incompetence resulting from
either technical error or probable late endocarditis, a second (chemically treated) valve being inserted. Eleven were available for review with the untreated valve still functioning 55 to 74 months postoperatively. Of these, all were symptomatically improved and seven were symptom free.

Five valves were available for histologic examination, the findings on which are to be reported separately. In brief, all the leaflets contained fibroblasts, the number varying with the duration of graft storage and the length of time it had been in the host. The collagenous and elastic tissue were well preserved, and there was no leaflet calcification. The specimen obtained 60 months after operation (fig. 3) had pliable cusps of normal thickness, with well-preserved elastic tissue and rather more fibroblasts than normal. The only calcification present was a small fragment adjacent to sutures in the graft aortic wall.

The aortic root calcification noted on cine film study was grade 2 in two patients with heavy valve calcification preoperatively and grade 3 in case 10 in which heavy syphilitic calcification was present preoperatively in the aortic wall.

Important incompetence was present in five valves. As noted above, three patients (cases 3, 4, and 5) required reoperation. In case 10, cineangiography demonstrated a peripheral leak in the suture line. With the exception of case 4, the degree of incompetence had not changed significantly over the years. Cusp rupture was not encountered.

The systolic pressure gradient across the valve was measured in 10 of these patients between 1 and 2 years or at an average of 59 months postoperatively or both. It was trivial in all instances and showed no significant increase between the early and late studies.

**Discussion**

This review of our first 101 patients allows a detailed and accurate assessment of the behavior of a homograft valve over a 4 to 6-year period. As three quarters of the valves were freeze dried and most were sterilized by beta propiolactone, the results relate chiefly to this method of valve preparation and storage. However, 16 of the earliest grafts were untreated (collected sterile and preserved in Hank's solution) so that these two methods can be compared.

The results indicate that all 71 surviving patients are symptomatically improved and 53, or approximately half the total number operated upon, have good functioning of the homograft valve. In six there is important residual incompetence with few or no symptoms, but in 12 survivors reoperation was required for valve failure. As a total of 19 patients were reoperated upon, and four others died from incompetence without reoperation, the valve failed completely in 23 of the 95 patients leaving the hospital (in 21 from incompetence and in two from stenosis).

Clearly the major cause of mechanical failure has been incompetence, although approximately two thirds of the patients leaving the hospital had absent or only trivial incompetence subsequently and, in the ab-

**Figure 3**

Gross fixed specimen of homograft valve removed surgically at 60 months because of severe incompetence, due to malplacement with prolapse of one cusp. Incompetence, was initially moderate but had increased slightly over the 5 years. Leaflets appear normal and microscopically there was good preservation of collagenous and elastic tissue and a slightly increased number of fibroblasts and no calcification. Homograft collected sterile and stored in Hank's solution for 5 days (see case 5 and table 8).
sence of cusp rupture or endocarditis, the degree of incompetence did not alter significantly over 4 to 6 years. Cineangiographic studies in 27 of these patients and in numerous subsequent patients, including a more recent consecutive series, indicate that in most instances a leak, when present, was peripheral. When this is the case the run-off around the valve is usually small and not clinically significant, although in this series, where the technic did not include aortic root tailoring, a major peripheral leak did occur in seven patients operated upon for severe aortic incompetence where there was a dilated aortic ring. When a central leak occurs, this is occasionally due to misplacement of the valve, in which case it is present from the time of operation, but more frequently it results from later cusp rupture. In this event severe incompetence invariably occurs and reoperation is required. Of the nine valves with cusp rupture, seven had been sterilized with beta propiolactone and freeze dried, one had been collected sterile and freeze dried, and one had been sterilized with beta propiolactone and stored in Hank's solution. The 10% rupture incidence with freeze dried valves is similar to the figure obtained in our subsequent patients and indicates that valves prepared in this way are unsatisfactory. The rupture incidence for valves stored in Hank's solution following sterilization with beta propiolactone appears to be about 5%, and the figure is similar with ethylene oxide sterilization. It is probably significant that rupture has not occurred with untreated valves although the numbers followed are small.

Central incompetence can also occasionally be due to late bacterial endocarditis. This is possibly more common if the valve is imperfectly placed, which can be compared to endocarditis on a congenitally deformed valve. For this reason, all patients with homograft valves should receive prophylactic antibiotics at the time of dental extraction and intercurrent infection. The endocarditis in these and in subsequent patients has been apparently cured with antibiotics, but it has almost always resulted in severe incompetence requiring reoperation. The incidence in this series is similar to that observed in subsequent patients.

Mechanical failure from stenosis has been rare, occurring in only two instances, where it was due to leaflet calcification. Cardiac catheterization has revealed minor gradients in only six of the other 22 patients studied 31 to 61 months following surgery and serial catheterizations showed significant progression in the degree of stenosis in only one of 14 patients, again secondary to calcification. There is certainly no evidence that untreated valves become progressively more stenotic than chemically treated valves from scarring and contracture of the graft aortic wall and myocardial remnant as found by Mohri and associates in the canine heart. Leaflet calcification is the only factor responsible for significant late stenosis in the present series.

This material throws some light on the late incidence of calcification in a homograft valve, although the significance of the data obtained with cinefilm screening of the heart for calcification is uncertain, as it is impossible to differentiate between calcium deposits in host and graft aortic wall. Four to six years after insertion significant calcification was present in the aortic wall remnant of the graft in two thirds of the specimens available, although it was never a cause of significant obstruction. When significant leaflet calcification was present, there was almost always a major exciting factor, as found by Davies' group, which was related either to imperfections in the original homograft valve, to errors in insertion, or to endocarditis. For good long-term function, not only must the valve itself be initially perfect, it must also be perfectly positioned, and when these criteria are fulfilled leaflet calcification would appear to be rare. Other factors probably affecting calcification are the method of valve preparation and the host's liability to dystrophic calcification. The incidence seems to be less in untreated valves, as none of these was affected, although it is also clear that a freeze-dried valve can remain calcium free for up to 70 months; in fact, half the freeze-dried valves.
examined had no calcification or only a trivial amount. The factors influencing the host liability to dystrophic calcification are unknown but are certainly important. For example, the rarity of calcific aortic stenosis among the Asian and Chinese people needs documentation and investigation. It may be significant that in this series all five patients with marked homograft leaflet calcification had heavy valve calcification before operation.

The causes of late mortality in the 24 patients differ from those reported with a Starr-Edwards aortic prosthesis. Thus, only one third of our patients died from valve failure compared with two thirds of the total late deaths in Herr and co-workers' series and about one half in the Mayo Clinic series. This difference is largely explained by the virtual if not complete absence of emboli from a homograft valve in this and other reported series and of deaths due to complications of long-term anticoagulation, which is not required with a homograft valve. It is also worth noting that, in contrast to thromboembolism and ball variance, homograft valve failure from whatever cause, including cusp rupture, has never resulted in sudden death, and reoperation with insertion of a second homograft valve is technically little different from the first procedure. While seven deaths followed reoperation on 19 patients in this series (two for stenosis and 17 for incompetence), four of these deaths were directly related to late referral of moribund patients. Now that cusp rupture is a recognized clinical entity, this seldom occurs.

Myocardial factors, including coronary atheroma, cardiomyopathy, essential hypertension, and arrhythmia, were the cause of 13 and probably 14 of the late deaths in this series. Coronary atherosclerosis accounted for five deaths in diabetic or elderly subjects, as well as being the probable cause of persistent angina in six others with good valve function. Primary myocardial disease or cardiomyopathy with progressive cardiomegaly and congestive heart failure despite good valve function and the absence of coronary atherosclerosis was the cause in six patients. It is possible that extensive myocardial fibrosis often associated with mural vessel disease may be irreversible in patients with long-standing severe aortic valve disease, despite correction of the valve lesion. The fact, however, that only eight subsequent patients have followed this course in the next 400 operations up to December 1967, suggests that coronary artery perfusion technics, particularly over perfusion, played a part in this early series. The data indicate that deaths due to myocardial factors were more common in patients with a large heart or a left axis deviation, although there was no correlation with symptomatic severity or age.

The current value of this review is limited by the fact that it represents our earliest experience of an original and difficult technic which has required modification as further experience has been gained. Firstly, alterations in the method of valve insertion, namely, additional sutures to obliterate most of the dead space between graft and host aortic wall and aortic root tailoring when the root is large, have virtually abolished significant leak around the graft. Secondly, important changes have been made in the method of homograft valve preparation, in the hope of diminishing cusp rupture and late calcification. Chemical sterilization results in a dead homeostatic graft with acellular leaflets which are not adequately supported or replaced by host tissue and may subsequently rupture. There is also a definite, although low incidence of important leaflet calcification within 4 to 6 years. Conversely, the untreated grafts stored in antibiotic Hank's solution have neither ruptured nor calcified and the one specimen examined at 5 years contained a near-normal number of fibroblasts. Because of these observations, valves are now collected as cleanly as possible by the pathologist and placed in Hank's solution, containing penicillin, streptomycin, kanamycin, and amphotericin B, for a minimum of 14 days at 4°C. While such grafts may not be vital, it is anticipated that cusp rupture will be rare and the long-term behavior superior to either chemically treated or irradiated valves.
Comparison of these results, in which 71% of all patients operated upon were alive 4 to 6 years later, with those achieved with other prosthetic devices is difficult, as no truly comparable data are available. Effler and associates, however, report that, with a Starr-Edwards aortic prosthesis, 53% of their patients leaving hospital were alive after 4 to 6 years; from the figures given by Cooley and associates, the 4 and 5-year survival for all patients undergoing isolated aortic valve replacement with a prosthetic device would appear to be approximately 51%. These comparative figures should be correlated with the fact that, after the fourth year, the homograft valve data show a decreasing mortality (fig. 2) and a minor morbidity from endocarditis and leaftlet calcification only. In contrast, the aortic ball valve data are reported to show a high late incidence of ball variance and a continuous morbidity from embolization and hemolytic anemia. It remains to be seen whether the changes in homograft preparation will further improve the long-term function of this graft and whether changes in ball-valve design will reduce the incidence of ball variance and thromboembolism and eliminate the need for anticoagulants.

Acknowledgment

Twenty-one of these patients were operated upon by Dr. D. S. Cole.

References

Aortic Homograft Valve Replacement: A Long-Term Follow-Up of an Initial Series of 101 Patients

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