Program for the 50th Annual McGuire Lecture Series

Cardiology in Primary Care

Presented by

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Friday, October 27, 1978

Exercise Stress Testing: Indications, Contraindications, Limitations
DONALD W. ROMHILT, M.D.

Thallium Myocardial Scanning
MICHAEL J. COWLEY, M.D.

Cardiac Catheterization: Indications in Coronary Disease
GEORGE W. VETROVEC, M.D.

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Surgery for Coronary Disease: Indications and Results
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Medical Management of Angina: Methods and Results
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Premature Ventricular Beats
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Mitral Valve Disease: When is Surgery Needed?
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Aortic Valve: When is Surgery Needed?
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Echocardiography
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INTRODUCTION

With this issue we continue the proceedings of the 50th Annual McGuire Lecture Series on Cardiology in Primary Care. In our Scripta Medica section we present a paper by Dr. James C. M. Chan on hyperuricemic nephropathy.

THE EDITORS
Results of Aortocoronary Bypass Surgery for Angina Pectoris

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SZABOLCS SZEINTPETERY, M.D.
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To determine the relative risks and benefits of coronary bypass surgery for angina pectoris, we examined the results in our first consecutive 360 patients operated upon between May 1970 and December 1975. The age range was 27 to 75 years; there were 309 males and 51 females. The patients were classified clinically as having stable angina in 119 cases (33%), unstable angina in 205 cases (57%) and preinfarction angina in 36 cases (10%). Unstable angina was defined as a definite recent increase in severity or frequency of chest pain, angina at rest or nocturnal angina. Preinfarction angina was defined as a syndrome of prolonged angina, poorly controlled by nitrates, occurring at rest with typical ECG changes of ischemia. Such patients underwent observation in the Coronary Intensive Care Unit followed by emergency arteriography and surgery, usually within 24 hours.

All patients had preoperative coronary arteriography and left ventriculography. Significant lesions were defined as 50% or more narrowing of the left main coronary artery and 75% or greater narrowing of the other vessels. Abnormal left ventricular function was defined as an ejection fraction of less than 40% and was considered severe if the ejection fraction was less than 25% or if a large left ventricular aneurysm was present. Forty-three patients (12%) had left main-vessel disease, 83 (23%) had single-vessel, 115 (32%) double-vessel, and 119 (33%) triple-vessel disease. One hundred and ninety-four patients (54%) had normal ventricular function and in 84 (23%) it was considered severe. Eighty-four (23%) patients had single bypass surgery, 135 (38%) patients had double bypass, and 140 (39%) patients had three or more grafts. One patient died in the operating room before bypass could be carried out. (See below.) Twenty-two patients (6%) had concomitant left ventricular aneurysm resection and are included in the analysis. Patients with angina pectoris were excluded from surgical therapy only if the left ventricular ejection fraction was less than 15% in the absence of a large left ventricular aneurysm or if there were no suitable vessels for grafting.

The operation (Fig 1) generally involved the use of the saphenous vein as the bypass conduit. When the greater saphenous vein was unavailable or inadequate, alternative choices included the internal mammary artery, lesser saphenous vein, and in two instances, Gortex synthetic grafts. Operation was carried out under hemodilution and moderate systemic hypothermia of 28 C to 30 C, using intentional ventricular fibrillation and intermittent aortic occlusion for periods not exceeding 20 minutes, or alternatively, cardioplegia with cold hyperkalemic...
solution for longer periods of arrest. When considered appropriate, coronary artery endarterectomy was carried out in addition to bypass grafting, most frequently involving the distal right coronary artery and occasionally the left anterior descending or circumflex branches. Aneurysm resection was performed in a standard fashion only when there was a full thickness scar with thinning of the ventricular wall; frequently, an intraventricular thrombus was removed during aneurysm resection.

**Results**

There were two operative deaths and four postoperative deaths within the first month for a total operative mortality of 1.7%. One operative death in a 54-year-old female with stable angina and two-vessel disease resulted from an iatrogenic intraoperative aortic dissection, with death occurring before extracorporeal circulation could be established. This was the only operative or postoperative death in the group of patients with stable angina. The second operative death was in the only patient who could not be weaned from cardiopulmonary bypass. Postmortem examination of the 62-year-old male revealed extensive three-vessel disease, an old anterior wall infarction, and a posterior wall infarction (suspected preoperatively) estimated to be of two to three days’ duration. No other patient required intraoperative or postoperative intra-aortic balloon assist. The operative mortality in the last four years of the study was 0.7%. There were four early postoperative deaths within one month: one from acute myocardial infarction occurring in a non-revascularized area one week after operation, one from acute renal failure in a patient with chronic renal disease, one from an unsuspected, ruptured abdominal aneurysm in an obese patient, and one from a dissecting aneurysm in a patient with severe myxedema.

During this same period of study, 33 patients had operations for valve disease and concomitant coronary bypass grafting with no operative or hospital deaths in this group. However, these patients were not included in the analysis of surgery for angina pectoris and are not further considered in this report.

**TABLE 1**

<table>
<thead>
<tr>
<th>Months after bypass surgery</th>
<th>Alive at beginning of interval</th>
<th>Died during interval</th>
<th>Withdrawn alive during interval</th>
<th>Estimated proportion surviving to end of interval (cumulative)</th>
</tr>
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<tbody>
<tr>
<td>0-6</td>
<td>360</td>
<td>9</td>
<td>27</td>
<td>0.974</td>
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<tr>
<td>6-12</td>
<td>324</td>
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<tr>
<td>12-18</td>
<td>277</td>
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<td>43</td>
<td>0.967</td>
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<td>18-24</td>
<td>233</td>
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<td>35</td>
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</tr>
<tr>
<td>24-30</td>
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<td>30-36</td>
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<td>36-42</td>
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<td>42-48</td>
<td>74</td>
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<td>24</td>
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<tr>
<td>48-54</td>
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<td>0</td>
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<td>0.905</td>
</tr>
<tr>
<td>54-60</td>
<td>28</td>
<td>0</td>
<td>14</td>
<td>0.905*</td>
</tr>
</tbody>
</table>

*Standard error of the five year survival proportion is 0.0248.*

Fig 2—Proportion of patients surviving following coronary graft surgery at the Medical College of Virginia from 1970 through May 31, 1976.
TABLE 2
Estimated proportions reporting angina free status following coronary bypass surgery at MCV from 1970 through May 31, 1975

<table>
<thead>
<tr>
<th>Years after graft</th>
<th>Angina free at beginning of interval</th>
<th>Symptoms returned during interval</th>
<th>Withdrawn angina free during interval</th>
<th>Cumulative proportion angina free at end of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>264</td>
<td>78</td>
<td>0</td>
<td>0.706</td>
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<tr>
<td>1-2</td>
<td>187</td>
<td>22</td>
<td>46</td>
<td>0.611</td>
</tr>
<tr>
<td>2-3</td>
<td>119</td>
<td>6</td>
<td>37</td>
<td>0.575</td>
</tr>
<tr>
<td>3-4</td>
<td>75</td>
<td>1</td>
<td>43</td>
<td>0.564</td>
</tr>
<tr>
<td>4-5</td>
<td>54</td>
<td>1</td>
<td>20</td>
<td>0.552</td>
</tr>
</tbody>
</table>

*Standard error for proportion angina free five years after surgery is 0.035.

Within the series of patients operated upon for angina pectoris, the perioperative infarction rate was studied in 100 consecutive patients with serial ECGs, vectorcardiography, and serum enzymes. A new perioperative infarction, one of which was fatal, was diagnosed in four patients.

There were 13 late postoperative deaths (3.4%) occurring two months to four years after operation; all were in patients who were classified preoperatively as unstable or having preinfarction angina. In each case there was abnormal ventricular function demonstrated preoperatively and in six patients it was considered severe. Two patients had aneurysmectomy in addition to bypass. Twelve of the 13 patients had documented myocardial infarction preoperatively. Ten of the patients had three-vessel disease and three of the patients two-vessel disease. Three of the deaths were non-cardiac in origin; one of disseminated malignancy and two from stroke. There have been no operative or postoperative deaths in patients with single-vessel disease. No late deaths have occurred during the period of this study in patients with a preoperative classification of stable angina pectoris. There were no operative or early postoperative deaths in patients with left main-vessel disease, and two late postoperative deaths have occurred in this group. Statistical analysis of all patients by life table methods (Table 1 and Fig 2), including the operative deaths, revealed a five-year expected survival rate of approximately 91%.

To evaluate the degree of palliation and its duration, follow-up evaluation was carried out in all surviving patients who had survived more than one year after operation at the time of the study. Evaluation consisted of personal examination, mail questionnaire, or telephone interview, with 100% follow-up. On the basis of the interviews, patients were classified as 1) asymptomatic, 2) improved, though with some angina, or 3) unimproved. An attempt was made to define when in the postoperative course angina

TABLE 3
Estimated proportions reporting improvement following coronary bypass surgery at MCV from 1970 through May 31, 1975

<table>
<thead>
<tr>
<th>Years after graft</th>
<th>Improved at beginning of interval</th>
<th>Failed during interval</th>
<th>Withdrawn improved during interval</th>
<th>Cumulative proportion improved at end of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>265</td>
<td>12</td>
<td>0</td>
<td>0.957</td>
</tr>
<tr>
<td>1-2</td>
<td>253</td>
<td>2</td>
<td>75</td>
<td>0.946</td>
</tr>
<tr>
<td>2-3</td>
<td>176</td>
<td>1</td>
<td>71</td>
<td>0.934</td>
</tr>
<tr>
<td>3-4</td>
<td>104</td>
<td>0</td>
<td>60</td>
<td>0.939</td>
</tr>
<tr>
<td>4-5</td>
<td>44</td>
<td>0</td>
<td>34</td>
<td>0.939*</td>
</tr>
</tbody>
</table>

* Standard error for proportion improved five years after surgery is 0.016.

Fig 3—Proportion of patients reporting improved status and proportion reporting angina-free status following coronary vein graft surgery from 1970 through May 31, 1976 at the Medical College of Virginia.
had reappeared or when therapeutic failure had occurred. Similar life table analysis of the duration of palliation (Tables 2 and 3, Fig 3) revealed that at five years 55% of the patients were anticipated to be pain-free and 93% asymptomatic or improved, with 7% either unimproved or worse.

Conclusions

These results appear to show that aortocoronary bypass grafting for angina pectoris can be carried out with relative safety and effectiveness in the majority of properly selected patients. The risk appears particularly low in patients with single-vessel disease, those with stable angina, and those with good left ventricular function. The operative risk also appears appropriately low for all patients with left ventricular ejection fraction above 15% so long as suitable graftable vessels are present even if concomitant ventricular aneurysm resection is required. Determination of the ultimate value of aortocoronary bypass grafting in terms of prolongation of life and duration of palliation will require several more years of analysis in view of the generally progressive nature of the disease both in the native circulation and in the bypass grafts. However, the analysis of this group of patients from one to five years after operation strongly suggests that operation has provided improved longevity as well as effective palliation.
Surgical Treatment of Mitral Valve Disease

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This paper discusses the indications for surgery in mitral valve disease by comparing the natural history of the disease, as it can best be determined from the literature, with the results of various surgical procedures. It may be stated at the outset, however, that there are no controlled studies comparing medical and surgical treatment nor are they likely to be carried out in the near future.

Mitral Stenosis

1. Detection. While the auscultatory findings of mitral stenosis are characteristic, many patients go undetected by routine clinical examination; it is, therefore, important to be aware of the special syndromes with which they may present (Table 1).

Mitral stenosis is much more common in women and should be looked for particularly in those who are young or middle-aged. The condition is predominantly a sequel to rheumatic heart disease which is prevalent among large families from lower socioeconomic groups. The availability of M-mode echocardiography in recent years has been of great help in the detection of mitral stenosis, since this procedure has nearly 100% sensitivity and the specificity is almost as good. With the two-dimensional echocardiogram the degree of stenosis can be measured with great precision by mapping out the valve area. Echocardiography has thus eliminated the need for cardiac catheterization either for the detection or quantification of mitral stenosis, and cardiac catheterization is now employed only preoperatively for the detection and assessment of associated lesions.

2. Natural history. Bland and Jones in their classical 20-year study of 1,000 patients with acute rheumatic fever showed the extreme variability in the rate of progression of mitral stenosis in different patients. Some patients developed mitral stenosis within 5 years after the first attack of rheumatic fever while others were relatively well even 50 years later; however, a composite average can be deduced from this and other studies. In the preantibiotic era, mitral stenosis was clinically detectable approximately 10 years after the onset of acute rheumatic fever, symptoms were minimal in the next 10 years unless pregnancy or complications occurred (for example, endocarditis or atrial fibrillation), and in the next 20 years symptoms increased progressively with development of pulmonary hypertension, heart failure, and systemic embolism, leading to death, approximately 40 years after the onset of rheumatic fever, at an average age of 48 (Fig 1).1-3

It is my impression that mitral stenosis today shows a slower rate of progression in the industrialized countries, mainly because the use of antibiotics has considerably improved the rate of recurrence of rheumatic fever and the treatment of endocarditis.

One of the most useful studies of the natural history of mitral stenosis is by Olesen and Baden who classified their patients according to the New York Heart Association (NYHA) classification and compared the non-surgical groups seen during the years 1933-1950 with the initial 165 consecutive patients operated on during the years 1950-1955 (Fig 2).4 Most studies of surgical treatment of mitral stenosis have

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TABLE 1
Some Presenting Syndromes in Mitral Stenosis

- EXERTIONAL DYSPNEA OR PULMONARY EDEMA WITHOUT GENERALIZED CARDIOMEGALY
- ATRIAL FIBRILLATION
- SYSTEMIC EMBOLISM (STROKE, MYOCARDIAL INFARCTION, HEMATURIA, ETC.)
- HEMOPTYSIS WITHOUT PULMONARY INFECTION
- RESTRICTIVE AND OBSTRUCTIVE LUNG DISEASE WITHOUT SMOKING HISTORY

used Olesen and Baden’s non-surgical patients for comparison. In NYHA Class II patients with normal sinus rhythm the ten-year survival was 80%. At the other extreme over 50% of Class IV patients were dead within five years and all were dead within eight years.

3. Choice of operations and results. The possibility of correcting the mechanical problem of mitral stenosis surgically was first discussed around the turn of the 20th century. The first attempts at surgical correction were made in the 1920s, but mitral valvotomy has come to be recognized as a generally acceptable method of treatment only since 1948. Today several different surgical procedures are available for the repair of mitral valve disease, some of the more common being listed in Table 2.

The operative and postoperative morbidity and mortality rates are very low for mitral commissurotomy but considerable when mitral valve replacement with a prosthesis is necessary. It is important, therefore, to determine preoperatively whether the patient with mitral stenosis will require commissurotomy or valve replacement. Table 3 gives some of the signs that determine this decision. Successful mitral com-

![Fig 1 — Natural progression of mitral stenosis. Clinical course, pathology and hemodynamic changes are correlated. Valve area is indicated below each diagram of valve. CO = cardiac output; Exer = exercise; LA = left atrial pressure; N = normal; PA = pulmonary arterial pressure; ↓ = decreased; ↑ = increased.](image-url)
Fig 2—Mitral Stenosis: Survival curves of surgery and medically treated patients. A. Normal sinus rhythm (NSR), NYHA Class II, B. NSR, NYHA Class III; C. Atrial fibrillation and NYHA Class II or III; D. NYHA Class IV. Vertical bars give 2 standard errors above and below each point.

Missuromy is not possible if significant regurgitation accompanies stenosis or if the valve is heavily scarred, markedly deformed, or calcified and immobile. Attempts at valvotomy in calcified valves result in fracture of the valve with resultant insufficiency rather than cleavage of the commissures. Lack of valve mobility is evident clinically by the absence of an opening snap and the presence of a muffled first heart sound; calcification can be detected by fluoroscopy and echocardiography. Repeated commissurotomies also cause extensive scarring and deformity which necessitate valve replacement.

Olesen and Baden showed that 'closed'

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**TABLE 2**

Common Operations Available for Mitral Valve Disease

- COMMISSUROTOMY
  - CLOSED
  - OPEN
- VALVE REPAIR
  - ANNULOPLASTY
  - VALVULOPLASTY
  - CARPENTIER RING
- VALVE REPLACEMENT
  - CAGE AND BALL VALVE
  - TILTING DISC VALVE
  - PORCINE TISSUE VALVE
mitral commissurotomy (that is, commissurotomy without cardiopulmonary bypass or 'open'-heart surgery) improved survival in all but minimally symptomatic patients in normal sinus rhythm. Long-term survival was adversely affected by the presence of preoperative pulmonary hypertension or postoperative mitral insufficiency. Ellis, Harken and Black reported essentially similar results in a much larger series of 1,000 surgical cases.

In the United States, most institutions use open mitral commissurotomy (that is, with cardiopulmonary bypass) as the procedure of choice for mitral stenosis. The results of open commissurotomy are probably superior to the closed operation, although it is a more expensive procedure. Improvements in surgical technique have markedly reduced the incidence of systemic embolization and mitral insufficiency, which were the principal dangers of mitral commissurotomy in earlier days. The mortality from mitral commissurotomy today is less than 1% when the operation is done at an optimal time and most survivors experience improvement in their symptoms.

When mitral stenosis can be treated with commissurotomy, the operation should be recommended as soon as symptoms interfere with the normal enjoyment of life or at the earliest signs of complications. In a substantial minority of patients, the valve restenoses after several years with recurrence of symptoms. Additional surgery should be considered in these patients.

The other types of mitral valve surgery will be discussed with the treatment of mitral insufficiency.

**Mitral Regurgitation**

The causes of mitral regurgitation are numerous; however, it is usually caused by congenital heart defects in young children, rheumatic heart disease or mitral valve prolapse in young adults, and coronary artery disease in older patients. The systolic apical murmur radiating into the axilla is usually easy to detect and is almost diagnostic of mitral regurgitation, although occasional patients with aortic stenosis have their murmur referred to the mitral area. Rupture of chordae tendineae to the posterior mitral leaflet may produce a murmur loudest at the sternum, simulating aortic stenosis. After mitral valve replacement, significant mitral regurgitation may occur silently but should be suspected if left ventricular failure or hemolytic anemia develops unexpectedly.

Detailed studies of the natural history of mitral regurgitation according to severity of the lesion or staging by symptoms are not available. Some impressions can be drawn from the prospective study of rheumatic fever by Bland and Jones. The prognosis of asymptomatic, mild, chronic mitral regurgitation without cardiomegaly is no different from that of the normal population; however, when significant symptoms are present with moderate-to-marked cardiomegaly, life expectancy is considerably shortened. In Rapaport’s experience approximately 20% of the patients with mitral regurgitation were dead within five years and 40% within ten years after their initial diagnosis.

Another consideration in mitral regurgitation regarding prognosis is the cause of the lesion. Most patients with mitral valve prolapse (click-murmur, Barlow syndrome) have a nonprogressive lesion. Mitral regurgitation secondary to chronic left ventricular failure and dilatation (for example, cardiomyopathy, hypertension) usually does not respond well to surgical treatment. In contrast with chronic mitral insufficiency, acute mitral insufficiency is very poorly tolerated and leads to rapid heart failure. Acute mitral regurgitation usually results from rupture of papillary muscles, chordae tendineae or valve leaflets due to infarction, infection or trauma, and occasionally spontaneously. In acute cases more attention should be paid to the severity of the hemodynamic lesion, as determined by physical signs and cardiac catheterization, than to the symptoms.

The combined lesion of mitral stenosis and regurgitation is usually due to rheumatic heart disease and is treated like mitral regurgitation because most patients require mitral valve replacement.

**Mitral Valve Repair**

The concept of repairing the valve instead of replacing it with a prosthesis is extremely at-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Signs Indicating Probable Need for Valve Replacement in Mitral Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• INTENSITY OF S3 OR OPENING SNAP REDUCED</td>
</tr>
<tr>
<td>• SIGNIFICANT MITRAL INSUFFICIENCY</td>
</tr>
<tr>
<td>• DENSE CALCIFICATION OF MITRAL VALVE</td>
</tr>
<tr>
<td>• PRIOR MITRAL SURGERY</td>
</tr>
</tbody>
</table>

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tractive, particularly for younger patients.\(^7\)\(^9\) It avoids the problems of thromboembolism, infection and hemolysis consequent upon the introduction of a foreign body into the bloodstream. The proponents of valve repair claim that it is feasible in a majority of patients with mitral regurgitation, but others have largely avoided it. Several different techniques have been described. Annuloplasty reduces the size of the valve orifice by plication of the annulus fusing the peripheral portions of the mitral commissures. Complete obliteration of mitral insufficiency is frequently not possible by this technique and postoperative dilatation of the mitral annulus may necessitate valve replacement at a later date. Valvuloplasty is a spectacularly successful and curative operation for many cases of ruptured chordae tendineae. The redundant untethered portion of the posterior leaflet is obliterated by pleating with sutures. The Carpentier ring is a slightly irregular biaurcuate stainless steel ring wrapped in a teflon collar for sewing which has been recently introduced as an aid to valvuloplasty. The ring prevents further dilation of the valve, and the sewing collar is used to anchor the sutures and remodel the deformed valves to approximate normal anatomy. Risk of thromboembolism and endocarditis is not significantly increased with the use of the Carpentier ring. At present, valve repair should be strongly considered in younger patients and in those with mitral insufficiency secondary to rupture of the posterior leaflet chordae tendineae. With continuing improvements in technique, valve repair is likely to become possible in a larger proportion of patients. The risk of valve repair is minimal, and marked symptomatic improvement occurs after successful surgery, but it is not possible to decide preoperatively whether repair or valve replacement will be necessary in a specific patient. The indications for valve repair are therefore the same as for valve replacement as discussed below.

**Mitral Valve Prostheses**

Three main types of prostheses are currently in use (Fig 3). Various models of the Starr-Edward heart valves are examples of the cage-ball type of prosthesis. Blood flows turbulently around the occluding ball in contrast to the laminated flow in the normal valve. Long experience

![Fig 3](image-url)
with these valves has shown them to be durable and reliable. The main problem is thromboembolism which is reduced but not eliminated by anticoagulants. Traumatic hemolysis may occur in models of the valve with cloth-covered struts. Another problem is the very loud closing click with some models. This sound can occasionally be heard by the unaided ear across the room from the patient. The incidence of infection of the prosthesis is probably similar to the other prosthetic valves.

Tilting disc valves, such as the Bjork-Shiley, have a more physiological blood flow and a low profile so that the valve does not occlude the left ventricular cavity. The major advantage of this valve is that the sewing ring is not disproportionately larger than the internal lumen and these valves are therefore associated with the lowest transvalvar gradients among all prosthetic heart valves. However, anticoagulation is needed and the closing click can be quite noisy. This is the prosthetic valve of choice in patients with a small mitral valve anulus.

Glutaraldehyde-treated porcine heterografts are becoming increasingly popular because of low thrombogenicity even without anticoagulation. These valves consist of porcine aortic valve tissue mounted on a man-made frame. Flow is central, very much as in the normal valve, but the sewing ring is considerably larger than the internal lumen, and large transvalvar gradients may be present postoperatively, particularly with the smaller-sized sewing rings. Long-term durability is another major concern. Nevertheless, this is the prosthesis of choice when anticoagulation is contraindicated.

Characteristics of the three valves discussed above are compared in Table 4.

Results of valve replacement. Comparative studies of different types of valve prostheses are not available at present. It appears, however, that the operative mortality for the different types of prostheses mentioned above is roughly comparable, and the risk factors for operative mortality and long-term results are also similar. The most important risk factors for early operative mortality are advanced heart failure and marked cardiomegaly, particularly left atrial enlargement (Fig 4).\(^6,10\) The long-term results are adversely affected in patients with marked left atrial enlargement or pulmonary hyper-

$$\text{TABLE 4}$$

Comparison of Three Most Commonly Used Prosthetic Heart Valves. Pros and Cons Graded from One to Three Plus. S-E = Starr-Edward; B-S = Bjork-Shiley; P-H = Porcine Hancock.

<table>
<thead>
<tr>
<th></th>
<th>S-E</th>
<th>B-S</th>
<th>P-H</th>
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<tbody>
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<td><strong>Disadvantages</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DURABILITY</td>
<td>+++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>LAMINATED FLOW</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>THROMBOEMBOLISM</td>
<td>+++</td>
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<td>HEMOLYSIS</td>
<td>+++</td>
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tension. Most survivors of the operation show symptomatic improvement, but their survival curve does not parallel that of the general population (Fig 5). Young patients with severe mitral regurgitation show a remarkable reduction in cardiac size following successful surgery, whether valve repair or valve replacement. Mitral valve replacement is recommended in all patients with significant symptoms, that is, NYHA Class III or IV. It is also indicated in acute severe mitral regurgitation and significant mitral regurgitation with progressive cardiomegaly or pulmonary hypertension, even when symptoms are less impressive (Table 5). It is advisable not to wait until advanced stages of heart failure, cardiac enlargement, or pulmonary vascular changes occur, but unfortunately patients are all too frequently in this condition when they first seek, or are referred for, valve surgery.

In summary, the natural history of mitral valve disease is discussed and compared with various surgical procedures. Life expectancy is considerably shortened when mitral stenosis is accompanied by significant symptoms or complications. Mitral commissurotomy is a relatively benign procedure (< 1% mortality) which improves survival and symptoms in these patients. Chronic mild mitral regurgitation is tolerated well, but progressive cardiac dysfunction occurs when regurgitation is severe, particularly if it develops acutely. Valve repair can be performed in some cases with a low mortality and very low postoperative morbidity. Most patients with incompetent valves require valve replacement in which the average surgical mortality is approxi-
Fig 4—Early operative mortality in isolated mitral valve replacement with Model 6120 Starr-Edward prosthesis, Mayo Clinic 3/66 to 1/72; A = mortality according to preoperative NYHA classification; B = mortality according to preoperative left atrial (LA) size.

Fig 5—Late survival and systemic thromboembolism in surgical survivors of isolated Starr-Edwards mitral valve replacement with model 6120 prosthesis compared to normal life expectancy.
TABLE 5
Indications for Valve Replacement in Mitral Regurgitation

- NYHA CLASS III OR IV
- SIGNIFICANT ENLARGEMENT OF LEFT ATRIUM OR VENTRICLE
- PULMONARY HYPERTENSION
- ACUTE SEVERE MITRAL REGURGITATION

mately 5%; thromboembolism is the most serious postoperative problem.

Surgical mortality is markedly increased in advanced heart disease (NYHA Class IV) and surgical treatment should therefore be considered in all patients with mitral valve disease before this stage is reached.

Figure 1 is taken in part from Proceedings of the Royal Society of Medicine (60:1009–1015, 1967) and the American Journal of Cardiology (35:221–227, 1975) by permission.

Figure 2 is adapted from the Scandinavian Journal of Thoracic and Cardiovascular Surgery (3:119–124, 1969) by permission.

Figure 4 adapts data found in Barnhorst et al., American Journal of Cardiology (35:228–233, 1975).

Figure 5 is adapted from the American Journal of Cardiology (35:228–233, 1975) by permission.

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Assessment for Surgery for Aortic Valve Replacement

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Surgical management of symptomatic aortic valve disease has been successful in improving both survival and function. Data reported from the literature suggest an operative mortality of from 5% to 8%, with a lower risk for elective replacement, and a 65% to 75% five-year survival rate as opposed to 50% to 60% in non-surgical patients with symptomatic aortic valve disease.

Aortic Stenosis

Valve replacement for aortic stenosis is usually indicated when angina pectoris, exertional syncope or congestive heart failure occur. Previous statistics suggest that with angina, which is the most common symptom, 50% of patients are dead within five years and with congestive heart failure, 50% are dead within two years, usually as a result of sudden death. In the adult, coronary disease is present in approximately half the cases of aortic stenosis. The etiology of angina may thus be multifactorial which makes this the most difficult of the major symptoms to assess. Obviously the severity of coronary disease influences subsequent survival; coronary bypass surgery at the time of valve replacement does not substantially alter perioperative mortality. At the present time a congenitally malformed bicuspid valve is the most common cause of aortic stenosis in the adult. Hemi-membranous aortic stenosis is now less common and occasionally calcific tricuspid stenosis ("aortic stenosis of the elderly") is seen.

Accurate clinical assessment of the severity of aortic stenosis may be difficult, especially in the elderly and in the patient with congestive heart failure. As cardiac output falls, the flow over the aortic valve diminishes and therefore the intensity of the murmur decreases. The usual physical findings with severe aortic stenosis include a narrow pulse pressure primarily because of decreased systolic blood pressure; a diminished carotid pulse volume with a slow rise to peak upstroke; a thrill often palpable in the second right interspace; and a murmur, most intense in the aortic area, typically of a crescendo-decrescendo type which peaks late in systole. An S4 gallop rhythm secondary to decreased ventricular compliance is audible. In the adult, the presence of an ejection click usually occurs only with pliable valves; the second sound may be diminished and becomes single as left ventricular ejection time increases. The electrocardiogram usually shows left ventricular hypertrophy. In the absence of congestive heart failure or concomitant multivalve disease, the chest X-ray reveals a normal heart size. The ascending aorta may be dilated secondary to post-stenotic dilatation, but the aortic knob is usually small as opposed to patients with generalized tortuosity of the aorta. Ordinarily the adult has valvular calcification which is seen better by fluoroscopy. The greater the calcification, the more likely the stenosis will be severe; thus fluoroscopy may provide useful information in selecting patients for catheterization. Single dimensional echocardiography reveals dense
Echoes in the aortic root but does not yield information on the severity of the valvular stenosis. The newer two-dimensional studies frequently allow one to determine a cross-sectional area, and show promise in the future of effectively selecting patients for catheterization by a non-invasive method when the clinical findings do not suggest severe stenosis.

Catheterization is the single best method to assess severity. With normal cardiac output, a large systolic gradient of greater than 50 to 70 mm Hg is usually seen with symptomatic stenosis. As cardiac output falls for a given fixed-valve area, the gradient falls; thus the valve area calculation is of major importance when the output is diminished. The usual aortic valve area is approximately 3 cm²; the calculated valve area determined by hydraulic formula, using the observed gradient and measured cardiac output, should be less than 1 cm² with symptomatic aortic stenosis and is less than 0.7 cm² with severe aortic stenosis.

The decision regarding replacement in the asymptomatic patient is not clear. Studies in children ages 2 to 21 with gradients greater than 80 mm Hg reveal that over a period of time the group operated upon was functionally better than the medical group; however, survival data were similar. These findings may not be similar in the adult; however, if the gradient is severe or if progressive electrocardiogram or chest x-ray changes occur then one might consider surgery.

**Aortic Regurgitation**

Chronic aortic regurgitation has a more varied etiology and, to a large extent, progression of disease is dependent on the cause. In general the murmur is detected years before symptoms occur, and because progression, even with a large regurgitant volume, is often slow, the decision regarding valvular replacement is often more difficult than with aortic stenosis. Years may pass before development of fatigability and then several years more until frank congestive heart failure occurs, resulting in an average survival of approximately two years after the onset of heart failure.

Acute severe aortic regurgitation secondary to endocarditis, aortic dissection or trauma usually leads to immediate surgery; thus the decision as to valve replacement is not as difficult as with chronic aortic regurgitation.

In brief, several features on clinical exami-

nation that suggest substantial regurgitation are widened pulse pressure with a low diastolic valve, bisferins carotid pulsation, rapidly collapsing peripheral pulses, and a displaced apical impulse. The absence of a diastolic pressure of less than 70 mm or a widened pulse pressure with the pulse pressure greater than 50% of the peak systolic in patients without congestive heart failure usually excludes severe aortic regurgitation. The rapidly collapsing pulses seen with chronic aortic regurgitation are also seen in high-output states and are not specific. The typical murmur is a decrescendo diastolic type which lengthens as the regurgitant fraction increases, that is, the longer the murmur, the more severe the regurgitation. The other auscultatory sign of significant aortic regurgitation is the presence of an Austin Flint murmur, that is, a middiastolic apical rumble which may be produced by turbulence because of closure of the mitral valve in diastole by the aortic regurgitant jet, with antegrade flow through the mitral valve, as 75% of the stroke volume may return to the left ventricle. A systolic flow murmur is often heard but is not helpful in assessing severity. An S3 gallop rhythm is common.

The electrocardiogram in severe aortic regurgitation should show left ventricular hypertrophy. The chest x-ray reveals a dilated left ventricle.

The echocardiogram usually shows a dilated left ventricle with shuddering of the anterior mitral leaflet because of the regurgitant jet but is generally not helpful in assessing severity. If the mitral valve closes prematurely because of very high left ventricular end diastolic pressure then this is a sign of severe aortic regurgitation; however, clinically there is little difficulty in establishing severity at that point. One study suggests that if the end systolic dimension is greater than 5.5 cm² then the incidence of subsequent complications is high and surgery may be indicated. These data have not yet been fully substantiated, and concomitant coronary disease or a myopathic process limits the value of this one finding.

Cardiac catheterization will yield information regarding hemodynamics and the degree of regurgitation.

The symptomatic patient is usually helped by valve replacement, but the decision to operate in an asymptomatic, or minimally symptomatic, patient with clinically severe regurgitation
is a difficult one. Ideally one would want a battery of noninvasive predictors such as an electrocardiogram, a chest x-ray, and an echocardiogram to predict the subsequent course and therefore to select the ideal time for surgery. Hirshfeld could establish no relationship between postoperative improvement or survival and preoperative heart size by x-ray, ECG, or New York Heart Association functional class. Spagnuolo found that in young persons with rheumatic aortic regurgitation 65% developed angina, heart failure, or died within three years if they had the combination of 1) diastolic pressure of less than 40, 2) cardiomegaly, and 3) left ventricular hypertrophy on electrocardiogram. With this triad of findings aortic valve replacement has been suggested.

Another consideration as to valve replacement for aortic regurgitation is that of preservation of myocardial function as in severe prolonged aortic regurgitation; irreversible myocardial changes may occur which cannot be corrected by surgery. The regurgitant volume will be eliminated by surgery and thus the patient may have symptomatic improvement, but myocardial function will remain poor; in addition the long-term survival rate with depressed left ventricular function is worse. In the future one would hope to replace valves at the point just prior to irreversible myocardial changes, but at present no tests are available to assess early irreversible changes accurately. Currently, exercise nuclear gated scans are being evaluated for exercise-induced wall motion abnormalities which may indicate early irreversible changes; the future of aortic regurgitation evaluation lies in assessing left ventricular function for timely valve replacement.

In summary, valve replacement is indicated for both symptomatic aortic stenosis and insufficiency. The prognostically important symptoms associated with aortic stenosis are angina, syncope or presyncope, or presyncope and congestive heart failure. The asymptomatic patient with aortic stenosis may be considered for valve replacement, but the long-term advantages of surgery in this group are not clear for adults. The symptomatic patient with severe aortic regurgitation is also a surgical candidate. The asymptomatic patient with clinically severe aortic insufficiency who has, or subsequently develops, left ventricular hypertrophy on electrocardiogram, with cardiomegaly and low diastolic blood pressure, may also be considered for valve replacement; however, the indications are not as clear-cut as with the symptomatic patient. In the future more emphasis may be placed on left ventricular function to determine early irreversible changes so that ventricular function may be preserved postoperatively. Arguments favoring earlier valve replacement are decreasing perioperative mortality, modification in prosthesis design to reduce long term complications, and higher perioperative mortality in the severely ill patients. The major argument against earlier valve replacement is that there is not yet an ideal valve; thus the potential for such complications as endocarditis, thromboembolism, and valve malfunction still exists.

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Recent Techniques in Echocardiography: Two-Dimensional Echocardiography

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Conventional M-mode echocardiography is a widely used noninvasive diagnostic technique. It allows bedside assessment of cardiac chamber dimensions, valve motion and left ventricular function. The limitations of this technique are that it (1) provides only a one-dimensional (icepick) view of the heart, (2) displays cardiac structures in an unfamiliar form that bears no resemblance to cardiac anatomy, and (3) does not provide information regarding spatial orientation of cardiac structures.

These limitations led to the development of two-dimensional (2-D) real-time echocardiography in the last decade. The 2-D echo allows simultaneous visualization of cardiac structures in real time through multiple planes.

There are two types of commonly used 2-D echocardiography:

1. Mechanical sector scanner. A single crystal transducer is mounted on a motor and oscillates in an arc of 30°. It is less expensive than the phased array scanner and can be interfaced with the existent M-mode echocardiograph. The disadvantages are noisiness, vibrations which the patient feels on the chest, and a narrow angle image. Newer, wide-angle mechanical sector scanners will overcome the last problem.

2. Phased array wide-angle sector scanner. This technique requires multiple elements in the transducer and there is a series of delays in the firing of the individual elements so that the ultrasonic wave front is at an angle to the transducer. By controlling the time sequence, the beam is electronically swept through a wide-angle sector.

The patient is examined lying supine or in the left lateral position with head slightly elevated. The echo information is recorded on a video cassette which can be stored and replayed later. The figures shown here are still frames of the cine.

The cardiac imaging is done in the following multiple views:

1. Parasternal long axis. The ultrasonic beam is parallel to the long axis of the left ventricle. Figure 1 is the anatomic section of the heart obtained in a presumed long axis plane of the left ventricle. Figure 2 shows the same structures seen with the 2-D echo. This view allows evaluation of pathology of the aortic root, aortic valve, mitral valve, and left ventricle.

2. Parasternal short axis. This view is obtained by rotating the transducer through 90° and provides tomographic sections of the heart from the apex of the left ventricle to the aortic root. Figures 3 and 4 show the anatomical and 2-D echo sections at the level of the papillary muscles; Figure 5 shows the 2-D echo sections at the level of the mitral valve. At this level the mitral valve area can be estimated by measuring the valve orifice with a planimeter during diastole. Figures 6 and 7 show anatomic sections and a still frame of a tomographic section of the sector scan at the level of the aortic valve.
Fig 1—Anatomic section of heart obtained in presumed plane of long axis of left ventricle.

Fig 2—Long axis view of left ventricle with 2-D echo in a normal subject. Head of subject towards right, feet towards left, chest wall at the top, and spine at bottom of figure. Anterior (AL) and posterior (PL) leaflets of mitral valve and posteromedial papillary muscle (PM) are seen. RV = right ventricle, LV = left ventricle, VS = ventricular septum, PW = posterior left ventricular wall, LA = left atrium, AV = aortic valve.

3. Apical four-chamber view. This view is obtained by positioning the transducer over the point of maximal cardiac impulse with the patient in the left lateral position. The ventricles are at the top and the atria at the bottom. Figures 8 and 9 are the diagrammatic and 2-D echo sections of this view.

4. Suprasternal view. The transducer is in the suprasternal notch and the ultrasonic beam im-

Fig 3—Anatomical section of heart along plane of ultrasonic tomographic section at level of papillary muscles.
Fig 4—Ultrasonic tomographic section of left ventricle at the level of papillary muscles (PM). Papillary muscles are seen at approximately 3 and 8 o'clock positions. RV = right ventricle, LV = left ventricle, VS = ventricular septum, PW = posterior left ventricular wall, LA = left atrium, AV = aortic valve.

Fig 5—Still frame of sector scan of short axis tomographic section of left ventricle at the level of mitral valve. In this figure, right ventricle is anterior and to the left. Left ventricle appears circular and is to the right. Anterior and posterior mitral leaflets have a fish mouth appearance during diastole. RV = right ventricle, LV = left ventricle, VS = ventricular septum, PW = posterior left ventricular wall, LA = left atrium, AV = aortic valve.

Fig 6—Anatomic section of heart obtained along presumed ultrasonic tomographic section at level of aortic valve.
ages the ascending aorta. This view is useful for the diagnosis of coarctation of the aorta.\textsuperscript{5}

**Contrast Echocardiography**

Contrast echocardiography is of value in detecting right-to-left shunt and tricuspid regurgitation. The usual contrast medium is a mixture of 5 ml of normal saline and 2 ml of air which are shaken together in a syringe to form microcavities then injected into a peripheral vein. An important precaution is to avoid injecting visible air bubbles. Two ml of green dye produce similar results. Figure 10 shows opacification of the right atrium, right ventricle, and pulmonary artery, following an injection of normal saline in a tomographic section at the level of the aortic valve.

**Clinical Application of 2-D Echocardiography**

The 2-D echo is still in the developmental phase and further investigations are required to establish its accuracy, sensitivity, and specificity. However, it has already made a significant contribution in the assessment of the severity of
mitral and aortic stenosis, regional and global abnormalities of the left ventricular wall motion, and congenital heart diseases.

**Mitral Stenosis**

Quantitative assessment of the mitral valve area with 2-D echo shows excellent correlation with the mitral valve area obtained by cardiac catheterization \((r = 0.95)\)\(^6\) and at operation \((r = 0.92)\).\(^7\)

**Mitral Valve Prolapse and Flail Mitral Valve**

Two-dimensional echocardiography has accurately defined patterns of mitral valve prolapse and flail mitral valve due to ruptured chordae tendinae.\(^8\)

**Aortic Stenosis**

Two-dimensional echocardiography not only localizes the level of aortic obstruction, that is, valvular, subvalvular or supravalvular\(^9\) but also allows noninvasive separation of significant from insignificant aortic stenosis. In our laboratory, patients with an aortic valve diameter of \(<1.3 \text{ cm (obtained in the long axis) and concentric left ventricular hypertrophy had a mean aortic gradient of } >50 \text{ mm Hg at cardiac catheterization.}\(^{10}\)

**Left Ventricular Wall Motion**

Regional and global left ventricular wall motion abnormalities can be studied noninvasively. The 2-D echo provides an ultrasonic angiogram of the left ventricle and thus left ventricular volumes and ejection fraction can be estimated. At the present time we still need validation of the accuracies and inaccuracies of the technique.

**Coronary Artery Disease**

There are reports of detection of left main coronary artery lesions with 2-D echo-
Further investigations are needed to define sensitivity and specificity of this technique.

**Congenital Heart Disease**

Two-dimensional echocardiography should prove helpful in delineating cardiac anatomy in critically ill infants who are at a high risk for cardiac catheterization as well as aid in the diagnosis of lesions such as atrial septal defects, ventricular septal defects, A-V canal defects, and transposition of great vessels.

In conclusion, the development of 2-D wide-angle echocardiography is a hallmark in the use of ultrasound as a diagnostic tool. It allows simultaneous visualization of cardiac structures in real time through multiple planes without known risk to the patient.

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Figures 8 and 9 are reproduced from Circulation (57:503-511, 1978) by permission of the American Heart Association, Inc.

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Management of the Difficult Hypertensive Patient

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Hypertension, while usually easily handled, can in certain patients present difficult problems in management.

Previous Neurological Disease

A history of stroke sometimes creates doubt as to the advisability of lowering the blood pressure as this might reduce flow to the brain, causing the patient to have another stroke. It is recognized that severe hypertensives clearly do better if they are treated, but the mild-to-moderate hypertensive patient with a history of stroke is a more difficult problem, and uncertainty about proper management has been so great that a large multicenter clinical trial—randomized, double-blind, and placebo-controlled—of 452 patients was done by the Stroke-Hypertensive Study group, and its results reported in 1974. All 452 patients had a history of a previous stroke and all had mild-to-moderate diastolic hypertension. This study showed that long-term outpatient treatment of the blood pressure neither caused nor prevented a second stroke. Other benefits such as a reduction in the number of episodes of congestive heart failure were evident in the treated group. It would seem, then, that patients with a history of stroke should be treated for their diastolic hypertension, unless there are other contraindications.

Isolated Systolic Hypertension

Another difficult problem is that of "isolated systolic hypertension," that is, blood pressure of 180/74 mm Hg, a condition common among older people.

Data from the Framingham study have shown that the age-corrected morbidity ratio is correlated with systolic or diastolic hypertension or both, as it is for stroke, congestive heart failure, and renal disease. Increased systolic blood pressure is therefore clearly a risk factor for cardiovascular damage, and one might assume that it ought to be lowered. Of the large, carefully conducted blood pressure treatment trials that show patient benefit (decreased death or morbidity), all required that patients have diastolic hypertension to get into the study and did not include those with such pressures as 180/74 mm Hg; these might have a stiff aorta and great vessels, requiring a high systolic pressure to pump a given stroke volume into the vascular system. In addition, treatment of the patient's 180 mm Hg systolic pressure will also lower the diastolic pressure, which may be undesirable. Symptomless coronary heart disease does exist, and blood flow through the coronary arteries is, of course, heavily dependent upon diastolic pressure, even more so in the presence of diseased arteries.

When encountering a patient with a wide pulse pressure or with a severe systolic hypertension and normal diastolic pressure, one should look for aortic insufficiency. Severe anemia, arteriovenous fistula, or thyrotoxicosis can also produce systolic hypertension.

Once these conditions are ruled out, the...
decision to treat or not to treat must be faced. Unfortunately, there are no data to indicate that such patients can be helped by treating their isolated systolic hypertension. In the face of this uncertainty, treatment is recommended only when the patient has clear evidence of definite cardiovascular damage that appears to be due to the hypertension per se; definite left ventricular hypertrophy might be present, for example, with no other explanation.

The systolic blood pressure usually rises with age in the American population which puts some millions of primarily elderly people at risk for untreated hypertension or at risk for treatment-induced complications. This is an important clinical problem that has not yet had the systematic and careful study which it deserves.

Mild Diastolic Hypertension

Whether or not to treat mild diastolic high blood pressure (96 mm Hg) may also cause uncertainty, but the Veterans Administration Cooperative Study Group, interpreted by Doctor Freis, has helped to clarify this question. If the diastolic blood pressure is high enough (over 104 mm Hg), one should go ahead and treat on the basis of the blood pressure alone. At lower levels, the presence of "risk factors" for hypertensive damage should be sought. These include the usual risk factors for atherosclerosis, such as hypercholesterolemia, diabetes, family history, obesity, among others, and age (youth), and race (black). If several risk factors for hypertensive damage are present, or if cardiovascular damage itself is already evident, one should treat the patient with borderline hypertension.

Lack of Response to Therapy

Occasionally, a patient may not respond to the prescribed medication. One reason for this might be incorrect cuff size. In dealing with an obese patient, this can be an important factor, causing as much as 10 mm Hg diastolic error, or more. Current recommendations of the American Heart Association are for a cuff (bladder) width "25% greater than the diameter of the arm"; thus, the standard cuff bladder, 12 × 22 cm, is suitable for a 10 cm (4-inch) diameter arm.

Other reasons why the patient may not be responding to treatment could involve technical factors. For instance, if the patient is engaged in conversation while the pressure is being taken, the diastolic blood pressure rises slightly. A cold room also raises the blood pressure, systolic and diastolic, as does recent cigarette smoking or an office "climate" that is rushed and hurried. A number of referrals have turned out to be patients who are able to recall that the office atmosphere in which their blood pressure was previously taken was hectic, or that they themselves were very rushed and hurried.

Another reason for non-response is that the patient may not be taking his or her medication. An estimated 25% to 50% of patients (depending upon definitions used) will be "non-compliant." Sometimes these individuals return regularly to see their doctor, even though they are not taking their medication; they may even count out the appropriate number of pills and throw them in the trash, so that the number remaining in the bottle appears to be correct to the physician. The best weapon against this is a good doctor-patient relationship in which the patient is assured of the physician's interest. For example, it helps to ask the patient if he or she is taking the prescribed medication regularly. If the answer is yes and the patient seems to be certain about it, the physician should inquire if the medication was taken on schedule that day and the night before. If the patient appears at all uncertain, the physician can then describe the difficulty created by not following treatment, and how this can inadvertently cause over-treatment. Patient education as to the nature of the disease and how complications are avoided has been carefully studied as a means to help compliance, but it has not been as successful as had been hoped.

Simplicity of treatment is very important. Most antihypertensive medications need only be taken twice a day at most. Drug combinations may help if the right combination can be found to fit the patient's needs.

A patient may be complying with prescribed medication and yet still not respond to treatment. The most common cause for this is subtle fluid retention. The body can retain anywhere from 5 to 11 pounds (depending on body size) of extra fluid without producing obvious edema that can be detected on physical examination; thus, a severe hypertensive should be weighed on every office visit. The extra fluid can be eliminated by salt restriction or by more powerful diuretics; this will often restore the responsiveness of the patient to the same program of
anthypertensive medication. Frank congestive heart failure also interferes with the response to medications, as does deteriorating renal function, when blood pressure medicines can become ineffective.

**Malignant (Accelerated) Phase of Hypertension**

Non-response to treatment may be caused by the fact that the patient is entering the malignant phase of hypertension; high diastolic pressures (130 mm Hg) will be present. This is, of course, a body-wide problem; the basic lesion, fibrinoid necrosis, occurs in arterioles all over the body. The condition can be diagnosed in the office by the following clinical manifestations:

1. Acute hypertensive retinitis or retinopathy: flame-shaped hemorrhages, and fluffy exudates, perhaps with papilledema.
2. Hypertensive encephalopathy: diffuse cerebral dysfunction, perhaps with somnolence, coma, and/or convulsions.
3. Malignant nephrosclerosis: microscopic or gross hematuria and proteinuria

These manifestations are totally curable by lowering the blood pressure to normal, unless the renal lesion has progressed far enough to produce gross decrease in renal function, at which point renal damage may be arrested or slowed, but not cured.

Once malignant hypertension has been halted, the prognosis is still poor. However, as long as the blood pressure is kept down, this syndrome will not return. Patients with newly-discovered malignant hypertension should be hospitalized for immediate control of the blood pressure.

**Secondary Hypertension**

Trouble may occur with pressure control when the patient has an unrecognized cause of high blood pressure. Pheochromocytoma is a classic example and these patients have notoriously erratic blood pressure that is very difficult to control. Coarctation of the aorta can cause real trouble as very satisfactory blood pressure levels may be produced below the coarctation and yet be uncontrollable above the coarctation. Perhaps the patient is on birth-control hormones which in some cases can cause pronounced hypertension. The possible use of artificial female hormones should be ascertained in women of childbearing age or even post-childbearing years.

**Severe Hypertension**

Severe hypertension can be difficult to manage. Hemodynamic studies have shown that these patients have normal cardiac output, normal heart rate, normal stroke volume, and normal cerebral blood flow unless they are in heart failure or severe renal failure. Subtle alterations in blood flow to several other parts of the body occur and renal blood flow is usually reduced. The small arterioles, because of their size, offer extremely high resistance to blood flow throughout the body. Treatment should begin with a diuretic, not because there will be an adequate response to the diuretic alone but because it decreases the amount of other medications that are required, and is therefore a reasonable foundation for therapy.

Hydrochlorothiazide is usually used, 50 mg twice a day, unless fluid retention is a problem, in which case furosemide is used; a low-salt diet can help, as can weight loss if the patient is grossly obese. It is extremely difficult to get a grossly obese patient to lose weight, but when successful, the weight loss will lower the blood pressure to a surprising degree.

Of course, other medications are going to be needed in addition to the thiazide. Methyl-dopa or propranolol could be added. Methyl-dopa is marketed as Aldomet. The highest dose that does any good in a large patient is a total of about 3.5 gm a day divided into two doses. Beyond that, little, if any, blood pressure change occurs and there is the possibility of an increase in toxicity.

Propranolol is marketed as Inderal and is a beta-receptor blocker. It affects not just the cardiovascular system but also blocks beta-receptors in the lungs and receptors in the endocrine system, so that there is the possibility of worsening of the asthmatic patient, or leaving the labile diabetic patient defenseless against hypoglycemia. It has recently been found that larger doses of propranolol are useful, and European and Australian physicians are using up to 1 gm per day if the patient needs it and can tolerate it well. We have not given quite this much at the Medical College of Virginia, but we are gradually moving to higher doses. Exactly
why propranolol has a good effect on the blood pressure in these high-dosage ranges (beyond what seems to do any good for angina pectoris) is something of a mystery. Propranolol is better tolerated in some ways than guanethidine, and causes less orthostatic hypotension.

Guanethidine is a useful and powerful antihypertensive but causes orthostatic hypotension, as well as intestinal and sexual problems. The dose is extremely variable, and must be individually adjusted, but nearly all hypertensive patients respond favorably to this drug. The problem is that it can produce intolerable side effects. Guanethidine and phenoxybenzamine given together have been shown to be useful in a few patients who do not respond to guanethidine and a diuretic alone.

If a patient is unresponsive to thiazide plus propranolol or guanethidine, a vasodilator may be added. Hydralazine is an excellent vasodilator and would be even more powerful if we could give enough. Long-term treatment must be limited to about 200 mg a day for an average-size patient because of a lupus-like syndrome that occurs at higher doses with disturbing frequency. I do not know of a single convincing case of lupus-like syndrome at MCV caused by less than 200 mg of hydralazine, and I have been looking specifically for it for the last twelve years.

Prazosin (Minipres) has been recently marketed as a vasodilator. There is some evidence that it has an additional alpha-blockade effect, but the exact balance between these two actions is not well known. It is useful up to 20 mg a day.

If all these drugs have been tried and the hypertension is still uncontrolled, hospitalization is indicated. At this time the physician can determine if any further action is required, such as an arteriogram, to eliminate the possibility of renal artery stenosis if the patient seems to be otherwise a reasonable surgical candidate for its correction. Hospitalization also presents an opportunity to look for other causes of hypertension that might be corrected. Under these conditions, it is always possible to control the blood pressure somehow, using parenteral medications. Later, the patient can be taken off parenteral medication and put on oral agents. The patient will usually be more responsive to the drugs, at least for a while, after hospitalization.

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Hyperuricemic Nephropathy: A Complication of Acute Leukemia in Children

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Introduction

In order to provide a point of reference for a rational approach to the therapy of acute uricemic nephropathy, the metabolic pathways leading to the production of uric acid will be briefly reviewed.

Uric acid is the end-product of adenine and guanine metabolism. Relevant to this discussion is the xanthine oxidase enzyme which catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid. In children with acute leukemia the increasing production and subsequent destruction of white blood cells result in the rapid elevation of uric acid concentration in the plasma, especially during treatment with antineoplastic drugs. This in turn may lead to the development of acute hyperuricemic nephropathy.1-4

The uric acid deposition in the renal medulla causes obstructive uropathies. This occurrence is not uncommon in children treated for reticuloendothelial malignancies, sarcoma and acute lymphocytic leukemia.

Incidence

The work done at the National Cancer Institute of the National Institutes of Health (NIH) showed that 6 out of 57 patients with acute leukemia developed uric acid nephropathy.4 The treatment had consisted of methotrexate, 6-mercaptopurine, hydrocortisone and cortisone. The duration of treatment before the clinical onset of hyperuricemic nephropathy was from three to six days. The maximum elevation of white cells was 11,800 to 18,000 per mm³; of uric acid from 17 to 71; and of BUN from 51 to 212 mg/100ml.

A number of subsequent reports have amply confirmed and extended these observations of Frei et al,4 and a number of conclusions can be made.

Risk Factors

Uric acid nephropathy is more prone to develop in the treatment of acute lymphocytic leukemia when the following conditions are present: elevation of white blood cells to more than 20,000/mm³, marked adenopathy, especially in the mediastinum, and massive hepatosplenomegaly.

The histology of severe uric acid nephropathy includes intratubular hydronephrosis and infarction from uric acid obstruction5,6; the milder and more common form of uric acid nephropathy shows marked renal enlargement produced by the intense interstitial leukemic infiltration; the glomeruli and tubules are intact. There is a good correlation between the kidney
and liver size in patients with less than 5% leukemic infiltration of these organs.\(^4\)

**Treatment**

The first two modes of treatment rely on the provisions of a more favorable situation for the deposition of uric acid which is reduced when the urinary pH is made alkaline in excess of 6, beyond which point the solubility of uric acid is increased in an exponential fashion.

To insure a good urine output, intravenous 5% dextrose/water is administered at a rate of 3000 ml/m\(^2\)/day. To promote uric acid solubility and therefore enhance excretion, the urine may be made alkaline by administering intravenous sodium bicarbonate at a dosage calculated to elevate the serum bicarbonate by 10 mEq/liter, and/or the use of a carbonic anhydrase inhibitor acetazolamide to block the renal tubular reabsorption of bicarbonate. The aims of these general measures are to achieve a urinary pH in excess of 6 and a urine volume in excess of 60 ml/m\(^2\)/hour.

If the urine output is less than 60 ml/m\(^2\)/hour after rehydration, mannitol (25% aqueous solution) is given initially over a 5- to 10-minute period in a test dose of 6.25 gm in children weighing less than 30 kg and 12.5 gm in children weighing over 30 kg. If diuresis ensues, additional mannitol is administered in the same dose every 6 hours to achieve a urine output of at least 60 ml/m\(^2\)/hour.

It is important to obtain and record urine volume, pH, body weight, vital signs, blood uric acid, electrolytes, BUN, and calcium concentrations every 12 to 24 hours.

Normal glomerular filtration rates are achieved within 2 to 14 days of treatment of hyperuricemia with fluids, bicarbonate and acetazolamide.\(^7\)

**Allopurinol**

Allopurinol (10 mg/kg/day initial oral dose) is a useful drug for the treatment of hyperuricemia.\(^7,8\) Allopurinol is a potent inhibitor of xanthine oxidase for which it is also a substrate.

Although the incidence of side effects is very low, the potential complications of allopurinol treatment should always be kept in mind. These include skin and blood dyscrasias, malaise, fever, complaints of nausea, headache, vomiting, vertigo, drowsiness and gastric irritation, muscle ache, elevation of SGOT/SGPT, leucocytosis, leucopenia and, rarely, peripheral neuritis and bone marrow depression.

**Special Therapy**

The rapid removal of uric acid can be achieved by either peritoneal dialysis or hemodialysis.

Peritoneal dialysis removes uric acid at a rate of 15 ml/min, but hemodialysis is at least five times more effective.\(^1,2\) The decision on when to institute these procedures is a clinical one and is based on the physician’s past experience and the patient’s status. One example of this complex clinical decision is shown in the Figure.

![Figure](image)

**Figure**—Acute uric acid nephropathy and treatment with hemodialysis is illustrated in the clinical course of a 14-year-old white boy.

Acute uric acid nephropathy occurred at the time of leukemic relapse. Diuresis did not occur despite all the general treatment procedures. Peritoneal dialysis was only partially successful in the removal of 4 gm of uric acid in 24 hours without lowering the serum uric acid concentration. Hemodialysis was instituted and removed over 17 gm of uric acid resulting in a decrease of serum uric acid from 87 to 29 mg/dl. Immediately following dialysis, he was given 25 gm of intravenous mannitol and was started on allopurinol. However, anuria persisted and a second course of hemodialysis was performed for 6 hours, resulting in a decrease of serum uric acid from 46 to 19 mg/dl. Just before the completion of the dialysis, he voided 340 ml of urine and the output remained adequate thereafter aided by good fluid and conservative medical management.
The use of hemodialysis is dependent on machine availability and the existence of a specially trained nephrology team consisting of dialysis technicians, nurses, surgeons, and nephrologists. Peritoneal dialysis requires less technical hardware and can be initiated more promptly by the nephrologist; whereas, before hemodialysis can be initiated, vascular access and somewhat extensive preparations are needed, especially in small children in the 2- to 3-year age group, where uric acid nephropathy more commonly occurs.

There is a relationship between the days of oliguria before dialysis has been started and the number of days until diuresis begins which has been taken as an indication for the early institution of either of these special procedures within a day or two of anuria and/or rapidly rising serum uric acid concentrations.

Summary

Hyperuricemic acute nephropathy occurs in 10% of patients with leukemia; the intrarenal uric acid deposition results in obstructive uropathy.

The clinical findings which point to the likelihood of renal damage are: first, an initial white blood cell count in excess of 20,000/mm²; second, marked adenopathy especially in the mediastinum; and third, the presence of massive hepatosplenomegaly. The aim of general treatment with fluids and renal alkalization is to promote uric acid solubility and output by maintaining urine pH in excess of 6 and urine volume in excess of 60 ml/m²/hr. The discovery and clinical use of allopurinol, an analogue of hypoxanthine and an inhibitor as well as a substrate of the enzyme xanthine oxidase, is central to the control of hyperuricemia. Allopurinol, as well as its metabolic end-product, alloxanthine, acts at the terminal steps of uric acid metabolism to reduce the production of uric acid and in conjunction with the other general medical therapy, contributes to the reversal of the hyperuricemia.

Finally, the special extrarenal procedures of peritoneal dialysis and hemodialysis can rapidly, efficiently and safely remove the uric acid from the body. The sooner one initiates either of these procedures, the earlier diuresis begins.

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REFERENCES

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And this growing involvement in a healthier, happier life is the most satisfying way we can imagine to demonstrate the world of opportunity still facing us here in Richmond.
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