coming through and have failed to demonstrate substantial benefits of GH treatment in patients with CHF due to dilated cardiomyopathy.  

We agree with Dr Dreifuss entirely—more in vivo and in vitro studies must be performed.

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Paclitaxel and Arterial Smooth Muscle Cell Proliferation

To the Editor:

I have recently completed reading “Paclitaxel Inhibits Arterial Smooth Muscle Cell Proliferation and Migration In Vitro and In Vivo Using Local Drug Delivery,” published in the July 15, 1997, issue of Circulation. My questions concerning this study are related to the claimed statistical significance of the in vivo data. According to the published methodology, the data were analyzed by a two-tailed unpaired t test. Having applied this test to verify the significance between the reported means, I find that none of the presented in vivo data have any statistical significance, and I am curious whether Axel et al, in error, might have used a paired t test.

Phillip F. Heller, PhD  
Laboratory of Cardiovascular Sciences  
National Institutes of Health  
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Response

We thank Dr Heller for his comments on our article. After reviewing the original data, we must admit that some statistical data of the in vivo part of the study were reported incorrectly. This was due to a misunderstanding between the statistician and the authors of the manuscript with regard to the probability values. Unfortunately, this error leads to statistical significance that does not exist in reality. However, we want to emphasize that the in vitro data were not affected by this error. The original data, the mean values, and the correct probability values are reported as follows in the Table. The correct probability values are $P=.18$ for mean intimal wall area, $P=.45$ for intimal wall thickness, and $P=.31$ for degree of stenosis. Therefore, paclitaxel applied with the microporous balloon was not able to inhibit intimal growth in this preliminary in vivo study. However, concerning the conclusion of our study, we have completed comprehensive experiments with the double-balloon catheter and paclitaxel in which we could show in vivo efficacy. The results have been submitted for publication. We sincerely apologize for the errors.

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Prospective Study of Asymptomatic Aortic Stenosis

To the Editor:

Relevant points were raised in the study of Otto et al on 123 adults with asymptomatic aortic stenosis and in the editorial by Carabello.  

We wish to endorse the crucial but neglected role of exercise testing in the management of patients with "asymptomatic" hemodynamically significant aortic stenosis. Stress testing is particularly pertinent before a decision is made to postpone surgical treatment. It is not only in the United States, as stated by Carabello, but also in the United Kingdom and in our own environment that there is some reluctance to exercise patients.

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Intimal Area</th>
<th>Intimal Wall Thickness</th>
<th>Degree of Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>Control</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>1</td>
<td>0.13 mm²</td>
<td>0.96 mm²</td>
<td>0.11 mm</td>
</tr>
<tr>
<td>2</td>
<td>0.15 mm²</td>
<td>0.31 mm²</td>
<td>0.08 mm</td>
</tr>
<tr>
<td>3</td>
<td>0.16 mm²</td>
<td>0.15 mm²</td>
<td>0.09 mm</td>
</tr>
<tr>
<td>4</td>
<td>0.46 mm²</td>
<td>0.29 mm²</td>
<td>0.11 mm</td>
</tr>
<tr>
<td>5</td>
<td>0.14 mm²</td>
<td>0.18 mm²</td>
<td>0.09 mm</td>
</tr>
<tr>
<td>6</td>
<td>0.20 mm²</td>
<td>0.2 mm²</td>
<td>0.12 mm</td>
</tr>
<tr>
<td>7</td>
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<td>0.12 mm²</td>
<td>0.2 mm</td>
</tr>
<tr>
<td>8</td>
<td>0.10 mm²</td>
<td>0.23 mm²</td>
<td>0.06 mm</td>
</tr>
<tr>
<td>9</td>
<td>0.30 mm²</td>
<td>0.81 mm²</td>
<td>0.15 mm</td>
</tr>
<tr>
<td>10</td>
<td>Thrombus</td>
<td>0.21 mm²</td>
<td>Thrombus</td>
</tr>
</tbody>
</table>

Mean ± SD  

| Intimal Area | 0.21 ± 0.11 mm² | 0.36 ± 0.29 mm² | 0.11 ± 0.04 mm | 0.14 ± 0.09 mm | 25.8 ± 8.0% | 33.8 ± 20.0% |

$P$ = .18  

$P$ = .45  

$P$ = .31
with aortic stenosis for fear that such patients were at high risk for complications during the test.” That philosophy is illogical when it is realized that such patients will inevitably exert themselves during their everyday lives, such as when late for an appointment or running for a bus. It is surely much safer to risk “complications” during or after a supervised treadmill test when adverse events can immediately be managed by experts and with appropriate facilities available. Several years ago we were referred an elderly colleague with tight calcific aortic stenosis who insisted that he regularly played 18 holes of golf without a golf cart. Exercise was stopped early on the treadmill because of depressed ST segments. Three minutes after effort, the heart rate decreased dramatically, the ST segments were depressed 6 mm, and the blood pressure was unrecordable. Elevation of his legs, administration of intravenous isoproterenol, and other measures reversed his parlous state. What would have happened on the golf course? This is anecdotal, but anecdotes remain instructive.

In the study of Otto et al., exercise testing was stopped in 60% of the “asymptomatic” patients because of “fatigue or shortness of breath.” The inference is that in at least some of these patients, the stress test should be judged to be abnormal. In a much smaller number, the definite abnormality of a drop in systolic pressure was detected. Exercise tests should be assessed not only for ST-T changes but also so-called “exercise variables.” Carabello stated that “ST-segment shifts during exercise do not constitute a positive test...” but “positive” for what? As further stated by Carabello, it is well known that many patients with tight aortic stenosis, left ventricular hypertrophy, and ST-T changes caused or exaggerated by exercise and who may or may not complain of angina have anatomically normal coronary arteries. This does not exclude the probability, however, that myocardial ischemia, whatever the mechanism for the inadequate coronary flow, is reflected in some instances by the ST-segment shifts.

Although any prognostic implication of these ST-T changes has not yet been clarified, we submit that it is their absence that is crucial significance in at least one important context. Children or young adults with tight aortic stenosis, invariably congenital (but occasionally rheumatic in our practice, where rheumatic valve disease remains highly prevalent), may be nearly asymptomatic, but there is always the consideration of sudden death. There is currently no operation, including the much-vaunted Ross procedure, that will last for 30 years, and surgery should clearly be postponed provided the patient’s life is not jeopardized. Such patients should be subjected to frequent maximal stress testing and, if ST segments remain normal or have minimal changes, there is to our knowledge no case documented in which sudden death occurred. The findings of Kveselis et al. are in accord with this philosophy.

Provided frequent exercise testing is undertaken, we agree with the overall conclusions of Otto et al. and Carabello that surgical management may be delayed justifiably in a number of patients with asymptomatic, or mildly symptomatic, aortic stenosis. We have several concerns with that policy, however. First, unduly rapid progression of aortic stenosis must be carefully sought in all patients. Second, any one of us may suffer a near-fatal vasovagal episode. We can only speculate on how many elderly, previously asymptomatic patients with aortic stenosis for fear that such patients who previously had no S-T segment depression during exercise but now has S-T depression on a repeat test should undergo valve replacement. I certainly concur and have long espoused that patients with left ventricular dysfunction caused by aortic stenosis normally derive great benefit from surgery. However, I would not agree with Drs Barlow and Jankelow that all patients should undergo surgery irrespective of the degree of left ventricular dysfunction. I believe that there remains a small group of patients with aortic stenosis undergoing coronary artery bypass surgery, especially when an internal mammary graft had been inserted, probably carries a twofold increase in operative mortality rates.

Last, Carabello correctly concluded that “prompt surgery is indicated” in symptomatic patients with severe aortic stenosis. We wish he had added “irrespective of the extent of left ventricular dysfunction” because, unlike some cases of aortic regurgitation, the postoperative result will always reflect some, and usually considerable, improvement.

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Response

I wish to thank Drs Barlow and Jankelow for their comments regarding my Editorial on “The Timing of Aortic Valve Surgery for Aortic Stenosis.” They point out that it is far more logical to exercise the patient with aortic stenosis under a physician’s supervision than to assume that a patient’s normal daily activities, which may involve considerable exertion, can be performed without risk. I entirely concur.

The issue of the meaning of S-T segment depression in aortic stenosis remains problematic. Many patients with left ventricular hypertrophy have S-T segment depression (“strain”) at rest. This occurs at a time when left ventricular function is normal and when coronary vasodilator reserve is not exhausted, suggesting that such depression does not indicate ischemia. Exactly what S-T depression means in aortic stenosis when it only occurs with exercise is also unresolved. While I concur with their assertion that the absence of S-T segment depression is reassuring, it is unclear to me that a totally asymptomatic patient who previously had no S-T segment depression during exercise but now has S-T depression on a repeat test should undergo valve replacement. I believe that there remains a small group of patients with aortic stenosis undergoing coronary artery bypass surgery, especially when an internal mammary graft had been inserted, probably carries a twofold increase in operative mortality rates.

I believe that there remains a small group of patients with severe aortic stenosis undergoing coronary artery bypass surgery, especially when an internal mammary graft had been inserted, probably carries a twofold increase in operative mortality rates.
Correspondence

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Response

Drs Barlow and Jankelow raise several interesting points, specifically the potential prognostic implications of ST-wave segment changes, the role of exercise testing in adults with asymptomatic aortic stenosis, and the optimal timing of surgery in patients with mild to moderate aortic stenosis undergoing coronary artery bypass grafting. In our prospective study of 123 adults with asymptomatic valvular aortic stenosis,1 the presence and severity of ST-segment depression during exercise testing did not correlate with clinical outcome, the presence or absence of coronary artery disease, or the severity of aortic stenosis. Even patients with mild aortic stenosis often had significant ST depression with exercise. However, the cause of ST depression in adults with only mild to moderate aortic stenosis remains unclear, and I share the concern of Drs Barlow and Jankelow that these abnormalities may represent subclinical myocardial ischemia.

The role of exercise testing also remains controversial. Although the exercise changes in cardiac output, stroke volume, systolic blood pressure, and valve area were all univariate predictors of clinical outcome in this patient population, the only multivariate predictors of outcome were aortic stenosis severity, the rate of change in aortic stenosis severity, and the patient’s functional status. In my view, because exercise testing does not add additional information regarding prognosis, it is difficult to justify routine exercise testing in adults with asymptomatic aortic stenosis. Also, it should be noted that although exercise testing can be performed safely in asymptomatic patients when monitored closely, we were careful to review possible symptoms with each patient immediately before the test and deferred exercise testing if any symptoms were present. Clinicians should be aware that the exercise test should be stopped promptly if blood pressure fails to rise appropriately because exertional hypotension may lead to serious complications, even with “asymptomatic” aortic stenosis.

The clinical decision regarding the optimal timing of surgery in adults with valvular aortic stenosis must consider the risks of surgery and a prosthetic valve as well as the natural history of the disease. It should be noted that there were no sudden deaths in our population, and cardiac deaths only occurred in patients with concurrent coronary disease and left ventricular dysfunction or those who refused aortic valve replacement. Thus we continue to defer valve replacement for aortic stenosis in adults until symptoms are present. However, it must be emphasized that a careful and detailed history is needed to elicit symptoms in adult patients. Given the gradual progression of the disease, many patients adjust their lifestyle as the disease progresses and may deny symptoms even when functional status is impaired. A careful discussion of the level of physical activity, comparison to prior levels of physical activity, and discussions with family members often are needed for recognition of the early symptoms of aortic stenosis. Clearly, in patients with severe aortic stenosis and decreased exercise tolerance, surgical intervention should be performed promptly rather than waiting for more severe symptoms.

The issue of aortic valve replacement in patients with mild to moderate aortic stenosis was not directly addressed in our study. I hope that the data on rate of progression will be helpful for physicians and surgeons making this decision in each individual patient.

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Prospective Study of Asymptomatic Aortic Stenosis
John B. Barlow and David Jankelow

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