authors state that they think the increase in responsiveness observed in their patients was simply the result of cigarette smoking, but they do not examine this question. Thus, the origin of the increase in responsiveness and its relationship to atopy and cigarette smoking are not clarified by their investigation.

The major problem with all existing longitudinal work published on increased responsiveness is that only subjects who already have COLD have been examined. At best, the Barter and Campbell and Kanner data can identify increased levels of responsiveness as a correlate of disease. At worst, their findings may simply be the result of selection bias. Although it is important to know that those subjects with COLD who have increased levels of airways responsiveness will fare poorly, a far more important question is whether one can identify the causes of increased levels of responsiveness, and its relationship to other putative risk factors, and whether such responsiveness is an independent risk factor for the development of COLD. This is a central question in adult COLD epidemiology at the present time for two reasons. First, if smoking causes increased levels of airways responsiveness, this will provide important insight into the pathogenesis of COLD. Secondly, it may target a group of subjects at high risk in whom therapeutic trials of bronchodilators might be used to attempt to intervene in the disease process. To determine whether increased level of airways responsiveness is a risk factor for COLD, one would have to follow prospectively a large cohort of subjects randomly selected from a community, some of whom smoked and some of whom did not, and assess respiratory symptoms, atopy, airways responsiveness and pulmonary function longitudinally over several years. Whether existing data are currently available with sufficient power to answer this question, or whether new studies carried out over several years will be required, the issue is of enough importance that a variety of methodologic approaches should be considered.

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Infected Endocarditis
Is Cardiac Catheterization Usually Needed Before Cardiac Surgery?

Cardiac surgery is now considered to be an essential part of therapy for certain patients with infective endocarditis. Uniform agreement exists that valve replacement is indicated for patients with severe heart failure due to valvular insufficiency or stenosis, patients with persistent infection (especially when due to yeast or coagulase), patients with severe peripheral destructive lesions such as annular erosions or myoccardial abscesses, and patients with dehiscence of prosthetic valves. Some authorities consider that demonstration of large vegetations by echocardiography and
When hemodynamic changes are not diagnostic of infective endocarditis, repeated catheterization may be justified to make the diagnosis. 1 Hemodynamic studies are also helpful for determining the optimal timing for surgical intervention. Patients who have persistently low cardiac output indices and who require additional transfusions to achieve low systemic pressures for more than 3 days should be considered for surgery to prevent the development of severe irreversible illness. Patients with recurrent embolization constitute an additional indication for surgery. 1

The indications for full cardiac catheterization prior to cardiac surgery during endocarditis are less certain. The paper by Hosenpud and Greenberg in a recent issue of Chest is one of only three studies that have attempted to define these indications. 2, 3 Hosenpud and Greenberg conclude that, "When there is any question of the accuracy of the clinical diagnosis, the patient's hemodynamic status or the need for additional indications for surgery, catheterization should be performed." Our opinion largely coincides with theirs, and is based in part on the potentially severe consequences of delaying a patient to cardiac surgery with an erroneous diagnosis.

Cardiac catheterization and cineangiography may be used to identify the site of infection, to define associated abnormalities such as myocardial abscesses or aortic root erosion, to determine the patient's anatomic status, or for incidental purposes such as to search for coronary artery disease which might benefit from simultaneous corrective surgery. Each of these indications should be examined separately. Ascertaining the sites of involvement in endocarditis is critical to planning surgical strategy. The majority of patients for whom surgery is suggested will have heart failure due to valvular insufficiency. Although physical examination is a sensitive and specific technique for detecting these valvular abnormalities, particularly when supplemented by noninvasive diagnostic studies such as echocardiography or radionuclide ventriculography, catheterization and angiography are still generally warranted. Even trivial valvular insufficiency may be an indication of infection at that site, and thus, is an indication for direct inspection at surgery. Hence, failing to detect an insufficient valve is a far more serious error than demonstrating valvular insufficiency which later is found to be unrelated to infection (eg, secondary to cardiac dilatation). In addition, it is difficult to assess the degree of valvular insufficiency when the heart is open and flaccid at surgery. If valve replacement is contemplated, it is useful to have angiographic assurance of hemodynamically severe valvular insufficiency, especially when there are other possible reasons for the observed congestive heart failure other than the valvular insufficiency. In patients who have a completely enigmatic focus of infection which is presumed to be intravascular—for example, persistently positive blood cultures with normal physical examination and echocardiography—selective quantitative blood cultures from multiple sites at catheterization may provide the only clue to the site of infection. 4 In our experience, the major limitation of this technique is that it is difficult to obtain statistically valid data (ie, showing a significant difference in the magnitude of bacteremias between cultures obtained upstream and downstream to the infected valve) in patients with low grade bacteremia (<10 colony forming units/ml blood).

Angiography also is useful for detection of invasive endocardial infection such as myocardial abscesses or aortic root erosions. Although the technique is not as sensitive as direct inspection at surgery, and many of these lesions can be suspected clinically or by echocardiography, there remain important lesions which would have been (or were) missed by all of these techniques unless angiography had been performed. 5, 6 Suspicion of coexisting coronary artery disease is also a valid indication for presurgical coronary angiography, and full cardiac catheterization with aortic root injection or ventriculography can easily be done at the same time.

The presence and degree of heart failure can be assessed satisfactorily by physical examination combined with measurements of pulmonary capillary wedge pressures, with added data from echocardiography (eg, demonstration of mitral valve preclosure in patients with aortic insufficiency) where needed. Full cardiac catheterization and cineangiography very seldom add anything to the evaluation of heart failure per se. 5, 6

Cardiac catheterization of the patient with active endocarditis should not be delayed or omitted because there is the risk of complications. All studies (and anecdotal clinical information) show cardiac catheterization and cineangiography in the presence of endocarditis to have an acceptably low risk of complications, probably little different from comparably ill patients without intravascular infection. 7, 8 Embolization due to fragments of vegetations dislodged by the catheter is the most obvious risk. In fact, this complication occurs rarely and can be further minimized by avoiding transvalvular catheterization (especially in the left heart) and reducing injection pressures.

Thus, we believe that the majority of patients with infective endocarditis who require surgery should receive preoperative evaluation by cardiac catheterization and cineangiography. The principal exception to this rule is patients with sudden, life-threatening rupture of the aortic valve that is obvious clinically, who may be sent to surgery without prior catheterization. At the present time, anatomic diagnoses supported by noninvasive means such as physical examination and echocardiography are not proved to be sufficiently accurate and complete in most patients with endocarditis to permit surgical intervention with confidence.

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Application of Clinical Trials to Clinical Practice

Design of developmental studies of a new pharmaceutical agent to produce the needed information is fraught with many hazards. Animals in long-term toxicology studies are unable to complain of subjective effects of the drug, and normal volunteers in the earliest kinetic and safety studies may be totally unrepresentative of the patients for whom the drug is intended. The first patients the drug reaches are either patients with very refractory problems who have not responded to conventional therapy or highly motivated patients who are interested in participating in a clinical trial. As these patients are generally more compliant and more willing to tolerate minor adverse effects than patients in clinical practice, trials in these patients may also not be representative of the efficacy and acceptability of the agent to the average patient. Therefore, it is essential to conduct trials which compare the new therapy to the conventional therapy for a given condition. However, these trials may be more difficult to perform than the initial trials in refractory patients. For example, qualified patients must not have failed the conventional therapy and so are usually less tolerant of adverse effects than refractory patients and also less willing to comply with a complex trial design.

Trials in refractory patients are usually performed first. In these patients a greater risk-benefit ratio is acceptable because they need therapy. If a substantial number of these patients respond to the agent, it is likely to be efficacious in a significant proportion of a less highly selected group. Comparing the agent to a placebo can demonstrate drug effect in refractory patients. Comparing the new agent to the best standard therapy, however, will yield information that is more applicable to clinical practice. Here the efficacy and patient acceptability can be assessed in a more typical, though still select, group of patients willing to participate in a clinical trial.

The best way to conduct a trial of conventional therapy compared to new therapy is a double-blind crossover trial. In an unblinded trial, the efficacy data may be objective and clear depending upon the end point, but adverse effect data, especially for a subjective problem such as sleep disturbance, is prone to bias. In trials comparing new and conventional therapy, it is also essential to compare doses that are likely to be widely used. Dose selection can bias the data toward efficacy or adverse effects, especially for agents with low toxic-to-therapeutic ratios such as the antiarrhythmics. Problems of bias secondary to dose selection can be avoided by comparing optimum doses of the agents, but this requires a more complex trial with a dose-ranging phase for each drug. This type of trial may provide the information that is most relevant to clinical practice. Nevertheless, data from an unblinded, carefully selected, single-dose trial such as that of Vlay and co-workers in this issue of Chest (see page 80) are important and provide a guide to the relative efficacy and patient acceptability of the conventional antiarrhythmic agent, quinidine gluconate and the new agent, lorcaidne.

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