Amiodarone therapy remains controversial with a diversity of opinion regarding its efficacy and toxicity, the usefulness of electrophysiologic studies for predicting long-term success and the risks and benefits of permitting its general availability. The drug is unique among cardiovascular compounds in its methods of entry onto the American scene; a number of important lessons are to be learned from the amiodarone saga. The traditional method of initial clinical evaluation of a new compound in this country occurs after a long research and development process by the pharmaceutical industry, the initiation of clinical trials after successful use in another country (usually also after a long research and development process) or the fortuitous discovery that a compound already in existence has beneficial cardiovascular actions. When a compound is ready for clinical trials the pharmaceutical industry sponsors the investigational new drug (IND) application at the Food and Drug Administration (FDA). Formal protocols are written with review of the overall scientific program by expert consultants from academia and clinical practice. Clinical trials are financially supported by the pharmaceutical industry and the drugs are carefully evaluated in a spectrum of studies. These studies typically include pharmacokinetic evaluations, studies in normal volunteers, hemodynamic and electrophysiologic evaluations, studies in patients with mild, moderate and severe disease and evaluation in life-threatening situations. Clinical monitors from industry prod investigators into collecting and recording data in a way that will provide meaningful information to support a new drug application at some future date. This system usually results in adequate accumulation of data regarding the pharmacology, efficacy, toxicity and clinical indications for a drug before its widespread use.

Early investigational studies on amiodarone. Amiodarone, on the other hand, has followed an entirely different course. Although at every step the intentions of investigators, industry and the government have been laudable and seemingly in the best interest of patients, the net result has been chaos and controversy often arising because of a paucity of scientific information. After encouraging reports from other countries (1,2), amiodarone was initially smuggled into this country by many of America’s foremost cardiologists in a valiant effort to benefit their patients. The process achieved legitimacy when a large number of individual IND applications were approved by the FDA and a major pharmaceutical company began to provide the drug free of charge. The United States Congress even got into the act by exempting the drug from the usual import tariffs, which had previously been paid by individual investigators from their own funds. At the time of its initial use in this country amiodarone was heralded as a miracle drug with little toxicity. However, the difficulty in obtaining the drug and the quasi-legality of its early use, investigators reserved it for the sickest patients after all other standard and investigational therapies had failed. Because of the critically ill nature of many of the patients and the lack of standardization provided by a coordinating pharmaceutical company, data collection was erratic.

Many early reports (3–5) about the efficacy, safety and role of electrophysiologic studies with amiodarone involved only a small number of patients with limited follow-up. Because many of the toxic side effects of amiodarone were unknown at the time, they may have gone unnoticed, having been attributed to the patient’s underlying disease process rather than the drug itself. Early reports indicated that some patients did well on amiodarone even though ventricular tachycardia remained inducible during electrophysiologic studies. This observation was attractive to many investigators caring for critically ill patients who had shown no improvement after treatment with multiple other standard and investigational drugs during electrophysiologic studies. A depressed patient who had been in the hospital for weeks could be given amiodarone and told that he or she would do well with this drug regardless of the outcome of electrophysiologic study. For many patients treatment with amiodarone provided an opportunity for hospital discharge that had not seemed possible before. Amiodarone was rapidly and widely heralded as being different from other antiarrhythmic drugs with regard to the value of intracardiac electrophysiologic studies for predicting long-term success and many centers even stopped doing electrophysiologic studies in patients receiving it (6).

Electrophysiologic testing: role in the amiodarone experiment. When one scientific experiment gives a different outcome from all others, one must examine the situation carefully to determine whether the theory behind all of the experiments or the individual discordant experiment itself is flawed. Several factors suggest that the flaw lies with the amiodarone experiment rather than with the theory that elec-
trophysiologic studies can predict long-term drug success.

1) The patients undergoing therapy with amiodarone are considerably different from those undergoing treatment with other antiarrhythmic drugs. Patients ultimately undergoing electrophysiologic testing with amiodarone have not responded to a number of other antiarrhythmic drugs during electrophysiologic testing and many drug responders have been withdrawn from testing before amiodarone is given. In fact, it may be that patients receiving amiodarone are a selected subgroup of patients in whom the ability of electrophysiologic inducibility or noninducibility of arrhythmia to predict long-term drug success somehow differs from that in the total patient group undergoing electrophysiologic study.

2) Typically, with drugs other than amiodarone, patients sent home on a regimen on which their arrhythmia remains inducible have a very high rate of early recurrence of arrhythmia with a flattening of the recurrence rate curve later in time. With all drugs a significant minority of patients will do well even though ventricular tachycardia is still inducible. Because in patients receiving amiodarone, the performance of electrophysiologic study may be delayed by several weeks or longer to be certain that amiodarone has accumulated, many patients with persistent clinical ventricular tachycardia may undergo electrophysiologic testing after very long periods or may not undergo electrophysiologic study at all, and are declared nonresponders on clinical grounds. Those patients remaining arrhythmia-free for several weeks while awaiting repeat electrophysiologic study may be a selected population biased strongly in favor of those who will do well even though their arrhythmia remains inducible. This group has, in fact, survived several weeks of a clinical trial before undergoing electrophysiologic study and may represent the flatter portion of the ventricular tachycardia recurrence curve. By analogy, if follow-up electrophysiologic studies were performed on patients receiving quinidine only after they had been treated successfully without a clinical recurrence of ventricular tachycardia for 2 to 4 weeks, a very high proportion of patients treated with quinidine might appear to do well despite inducible arrhythmia.

3) Because of amiodarone’s pharmacokinetics, intermittent noncompliance during long-term therapy may play a smaller role in arrhythmia recurrence than it does with other antiarrhythmic drugs. As many as 10 to 15% of long-term antiarrhythmic drug failures may be secondary to intermittent noncompliance. Removal of this factor for amiodarone probably plays a role in permitting a higher proportion of patients receiving this drug to do well when compared with patients receiving other antiarrhythmic drugs with a shorter half-life and less total body accumulation.

4) In some recurrences of ventricular tachycardia during amiodarone therapy, the rate may be slower and the arrhythmia not readily appreciated by the patient. Although this may indicate a clinically successful outcome of therapy, failure to detect asymptomatic episodes may bias the long-term predictive value of electrophysiologic studies.

5) Most studies establishing the role of ventricular tachycardia inducibility for predicting the long-term efficacy of drug therapy have utilized careful life-table analysis of long-term recurrence and statistical assessment of the role of inducibility (7). The majority of early studies reporting on amiodarone (3,4,8,9) failed to apply these standard techniques. In fact, several more recent studies utilizing techniques of discriminant analysis and life-table analysis have indicated that ventricular tachycardia inducibility during electrophysiologic study in patients receiving amiodarone may well be a powerful predictor of arrhythmia recurrence and long-term outcome (10,11).

**Electrophysiologic versus noninvasive monitoring studies to identify patients at high or low risk for arrhythmia recurrence.** Operating under the possibly false assumption that ventricular tachycardia inducibility during electrophysiologic study has no value, two studies in this issue of the Journal (12,13) attempt to define other electrophysiologic or electrocardiographic findings that will help to define long-term drug success. After examining these studies one is struck by the overall poor amiodarone success rate of amiodarone. In the study by Naccarelli et al. (12), 14 (40%) of 35 patients had a clinical recurrence of arrhythmia with a follow-up period of just over 1 year and in the study by Veltri et al. (13), almost 50% had a clinical recurrence by 1½ years. These high failure rates may reflect the finding that many patients receiving amiodarone (in fact, all of the patients in the study by Naccarelli et al.) remain with ventricular tachycardia inducible at electrophysiologic study. Both studies do provide important information to help identify patients at high and low risk for long-term arrhythmia recurrence. These two studies, however, examine entirely different patient populations. The patients in the study of Naccarelli et al. were selected for repeat electrophysiologic study with amiodarone alone only if they had nonsustained ventricular tachycardia suppressed on noninvasive monitoring. Thus, their patients would seem similar to the “ventricular tachycardia absent” patient discussed by Veltri et al. Taking these studies at face value, one might suggest a clinical approach to patients treated with amiodarone. If nonsustained ventricular tachycardia persists during noninvasive monitoring, amiodarone is unlikely to succeed. For those patients free of nonsustained ventricular tachycardia, an electrophysiologic study can be performed. If no ventricular tachycardia is inducible, patients are likely to do well (10,11). If ventricular tachycardia remains inducible the criteria suggested by Naccarelli et al. can be applied to select those who would do well and should remain on drug therapy. The patients with persisting nonsustained ventricular tachycardia on noninvasive testing or those predicted to do poorly by the criteria of Naccarelli et al. can be selected for automatic defibrillator implantation or other surgical
therapy. Before widespread application of this approach, however, prospective studies must be performed utilizing these retrospectively determined criteria to test their validity.

One final point seems worth making. The data analysis carried out by Veltri et al. utilizing sensitivity, specificity and predictive accuracy is less valuable than it would seem at first glance. This type of data analysis is most suitably used to examine the value of a test with an immediate outcome such as the ability of the exercise treadmill test to predict the presence or absence of coronary artery disease at an angiographic study. It is not well suited to the assessment of long-term antiarrhythmic drug outcome since there is no way to control for duration of follow-up. The percent predictive accuracy will be different depending on the duration of follow-up. The analysis would be improved if one compared the percent predictive accuracy at 1 and 2 years of various tests or, better yet, limited presentation to the use of life-table techniques.

The future of amiodarone. Regardless of our ability to predict long-term outcome, the ultimate value of amiodarone may be seriously limited by its significant toxicity. The lack of a coordinated central effort sponsored by the pharmaceutical industry to tabulate the precise incidence of drug toxicity due to amiodarone has led to an ad hoc movement among a number of investigators to form the Amiodarone Toxicity Study Group. It is hoped that this data collection being coordinated through the Cardiology Division at the University of Utah will provide meaningful data concerning the long-term toxicity of amiodarone.

The evolution of the amiodarone story in the United States indirectly lends a strong note of support for the much maligned drug evaluation and approval process in this country. Although we frequently have industry pointing fingers at the FDA, FDA pointing fingers at industry, investigators pointing fingers at both industry and the FDA and consumer advocates pointing fingers at everyone, nonetheless, the imperfect process that does exist generally provides a firm scientific basis on which rational decisions can be made regarding the efficacy, toxicity and clinical indications of a new drug. Failure to follow these traditional avenues has resulted in an unfortunate situation where investigators, industry and government feel compelled to do something, yet no one knows precisely what to do. Caught in the middle are the thousands of patients currently receiving amiodarone and at risk are the tens of thousands of patients who might, in fact, be harmed by the wrong decision. Although it seems at this time almost too late to begin anew with amiodarone, the lesson learned is obvious and the same mistakes should not be repeated in the future.

References