SUDDEN CARDIAC DEATH AND CONGESTIVE HEART FAILURE:
DIAGNOSIS AND TREATMENT

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PREFACE

In March of 1980, we organized the first symposium on how to evaluate new antiarrhythmic agents in which the participants included members of the Cardio-Renal Division of the Food and Drug Administration, academic investigators from the United States and Abroad and directors and implementors of pharmacological research representing the pharmaceutical industry. By bringing together all three elements, it was hoped that better communication and understanding would ensue to more rapidly bring new cardiac agents to the American public. This goal was important since a rather limited number of antiarrhythmic agents were and are currently available to treat patients with such disorders in the United States. These agents are needed not only for the treatment of patients with sustained ventricular tachyarrhythmias which produce life-threatening hemodynamic consequences but also and in fact more potentially important as a prophylactic measure in the high risk patient subject to sudden cardiac death.

This book represents the proceedings of the third of these Symposiums whose purpose was to evaluate the clinical research methodology and models used in the evaluation of new antiarrhythmic agents for not only acute therapeutic intervention but also for the prophylaxis of sudden cardiac death. In addition, new devices have evolved over the past few years that can detect and treat life-threatening cardiac arrhythmias and the evaluation of efficacy and safety of these devices is detailed. Finally, the therapy of new pharmacologic agents that impact upon the treatment of chronic congestive heart

failure was addressed. It is hoped that the availability of these new agents can add to the treatment regimens of patients with heart failure and prove to be of therapeutic benefit.

This symposium was organized by investigators without reference to political or offical advisory status and the funding was achieved by educational grants from over two-dozen members of the health care and pharmaceutical industries.

The following chapters represent the collective efforts of physicians and scientists from the United States and Abroad as well as members of the Food and Drug Administration to address these problems. State of the art positions are presented by noted authorities and discussion sections highlight the viewpoints and concensus opinions of the symposium participants about the important topics raised. While no unanimous concensus was expected to evolve from such discussion, the following pages will identify important research questions and clarify particular inter-relationships between different study models hoping to answer these questions. We would expect that this book will be used as a reference for those interested in study designs and guidelines to determine the suitability of projects attempting to define therapeutic efficacy and tolerance of new antiarrhythmic agents, new antiarrhythmic devices and new agents in the treatment of congestive heart failure.

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DO ANIMAL MODELS PREDICT RESULTS IN MAN?

E. Neil Moore D.V.M., Ph.D. and Joseph F. Spear, Ph.D.

No single experimental animal model is adequate to define the probability of antiarrhythmic efficacy in man. However, by utilizing a series of animal models for the evaluation of new antiarrhythmic agents it is possible to predict with assurance that a compound will have antiarrhythmic activity. The problem in finding useful new cardiac drugs is not in identifying agents with good activity but rather in finding antiarrhythmic activity without undesirable side effects.

Numerous monographs have been published which deal extensively with both acute and chronic arrhythmia models and their ability to evaluate antiarrhythmic agents (1-13).

In this paper we will discuss some of the models that have been most often used to evaluate new cardioactive drugs. The ability of any model to predict antiarrhythmic efficacy of a new agent relies primarily on comparing its effects with known antiarrhythmic agents in the model.

Isolated tissue studies have played the major role in our understanding of the mechanisms for cardiac arrhythmias and antiarrhythmic activity. Until recently it was thought that most arrhythmias were due to alteration of normal cardiac automaticity or alterations related to simple circus movement reentrant phenomenon. The demonstration that slow channel currents give rise to slow responses, triggered automaticity, and after depolarizations (13,14), and the demonstration of reflection (15), a type of reentry which does not require unidirectional block, have not only

expanded the possible mechanisms of cardiac arrhythmias but have also complicated the evaluation and design of cardiac antiarrhythmic agents. The fact that there are so many potential mechanisms associated with cardiac arrhythmias and that more than one mechanism can cause arrhythmias in the same heart complicates antiarrhythmic therapy.

The most frequently studied effects of antiarrhythmic agents using isolated tissues have been performed using normal ventricular muscle and/or free running Purkinje fibers removed from canine, ungulate, feline, guinea pig and rabbit ventricles. The standard parameters measured are the resting membrane potential, the action potential amplitude, the maximum rate of depolarization, action potential duration and rate of diastolic depolarization. Membrane responsiveness is determined by evaluating the maximum rate of depolarization as a function of the membrane potential from which the action potentials is evoked (1-4).

Conduction velocity important in reentrant arrhythmias. Since the amplitude of the action potential and the rate of depolarization of the action potential both influence conduction velocity the effects of antiarrhythmic agents on the fast inward sodium current responsible for depolarization and action potential amplitude have been evaluated for numerous antiarrhythmic agents (2). Shifts in the membrane responsiveness curve reflect an effect on the inactivation-reactivation kinetics of the sodium current. Another factor that plays a major role in circus movement reentrant arrhythmias is the refractoriness of the tissue. The action potential duration helps predict refractoriness of the tissue. Refractoriness is associated not only with inactivation-reactivation of the fast sodium channels, but also with the ionic conductances responsible for repolarization which are primarily potassium currents (4). Thus a qualitative estimate of the effects of an antiarrhythmic agent on depolarization currents and also on recovery current kinetics can be recorded with simple transmembrane potential recording of action potentials. However, for more quantitative analysis it is necessary to use voltage clamp techniques which allows specific currents to be directly monitored or the newly developed ion specific potassium, sodium, and calcium microelectrodes.

It should be pointed out that the mechanism of action of an antiarrhythmic drug may be such that its effect cannot be detected using a standard <u>in vitro</u> preparation. For example, the antiarrhythmic mechanism

may be due to alterations of autonomic tone or to drug metabolites. The failure of some drugs to have the same effect at the same concentrations in vitro as they do in vivo is also poorly understood. The finding that other antiarrhythmic agents such as amidiarone require a time period before their antiarrhythmic action develops further limits the use of isolated tissues for study of certain antiarrhythmic agents.

Only within the last 10 to 15 years have studies on isolated cardiac tissues routinely been completed using cardiac tissues made abnormal in many different ways including ischemia, superfusion with drugs (digitalis), altered potassium and calcium concentrations,the addition of catecholamine, stretch, altered blood gases and maintained depolarizing current (12,13). These alterations can change normal automatic mechanisms as well as bring out triggered automaticity and other mechanisms of automaticity that are not characteristic of normal fibers. Triggered activity can be distinguished from other types of enhanced automaticity since triggerable fibers will remain quiescent unless activity is evoked by an exogenous source, i.e. a premature beat. Since there are so many recently discovered mechanisms for arrhythmogenesis that can only be directly demonstrated using microelectrode techniques, cellular electrophysiology models should play a role in antiarrhythmic drug evaluations.

The evaluation of antiarrhythmic agents in acute coronary ligation models is complicated by numerous factors including the inability to predict the time of onset of arrhythmias or even whether arrhythmias will or will not develop. Therefore measurements of arrhythmias cannot be repeated in a reproducible fashion. In addition, although electrical stability may return following release, mechanical deficiencies still often remain. The recent demonstration of 2 periods of arrhythmias, one at 2 to 12 minutes and another at 13 to 30 minutes after occlusion also complicates the acute occlusion models (17,18). Variability in the efficacy of antiarrhythmic agents in the acute coronary ligation models is influenced by whether the drug is administered prior to or at the time of occlusion. Other factors which influence efficacy are how proximal the vessel is occluded, manipulation prior to occlusion, neurohumoral state, anesthesia, and blood electrolytes. Also, antiarrhythmic efficacy with bolus intravenous administration may differ from oral administration where metabolites as well as selective tissue accumulation of the drug can

influence antiarrhythmic effects. Although acute coronary occlusion ligation models are not ideal, they still have been most helpful in predicting antiarrhythmic efficacy. In many cases they may even be too severe a test since higher blood levels are usually required to depress ventricular tachyarrhythmias in these models than have been found to be effective in man.

Harris demonstrated nearly 30 years ago that if the anterior coronary artery is ligated in a two-stage procedure that most dogs survive the acute procedure and that 24 to 72 hours after the occlusion there is a high incidence of spontaneous arrhythmias (17). These arrhythmias which last up to 72 hours are rarely accompanied by ventricular fibrillation. Their mechanism is different from that of the ventricular arrhythmias of the acute ligation period (9). Purkinje fibers removed from the infarcted region 24 hours after coronary occlusion exhibit enhanced automaticity and in studies using mapping and stimulating techniques in anesthetized dogs these arrhythmias have been found to originate from the surviving subendocardial Purkinje system overlying the infarcted myocardium. These arrhythmias may be overdriven by electrical pacing and can be unmasked by slowing of the heart rate by enhanced vagal tone. While reentrant arrhythmias may be induced during this period, the predominant rhythm disturbance appears to be due to enhanced automaticity in the Purkinje system. In humans, arrhythmias that occur during this period after myocardial infarction may have a similar mechanism (9,12).

The 2-stage Harris ligation model probably is the most commonly employed coronary infarction model for evaluating new antiarrhythmic agents. In many instances it is a very severe test of a new antiarrhythmic agent in that drug levels necessary to suppress the ectopic rhythms in this model are higher than those required for suppresion of ectopic activity in man. This may relate not only to the differences in mechanism underlying the arrhythmias but also to species variations. The marked variability in the percent of ectopic beats that occur in the 2-stage Harris coronary ligation model is often not taken into account when evaluating antiarrhythmic efficacy. For example, in some instances, nearly 100% of the beats may be ectopic whereas in others less than 50% will be abnormal. It is difficult to evaluate whether or not the model with the higher incidence of ventricular tachyarrhythmias is a more severe test than animals exhibiting fewer PVC's. In addition to a variation in

the percent PVC's there also may be a marked variability in the actual heart rate. Heart rate can influence the type of arrhythmias as well as their severity. In fact it is possible by altering heart rate to eliminate tachyarrhythmias. Thus, the statistical evaluation of the suppression of ventricular tachyarrhythmias by an antiarrhythmic agent in the Harris 2-stage ligation model should take into account variabilities in heart rate and percent PVC's among animals as well as the spontaneous variabilities that occur with time in each animal.

Chronic animal models having electrically inducible ventricular tachyarrhythmias similar to the lethal ventricular arrhythmias that contribute to sudden death in patients with ischemic heart disease have proven very difficult to develop. However, recently several laboratories have found that the use of occlusion-reperfusion and multiple ligation of distal coronary arteries can result in the canine and feline hearts having ventricular tachyarrhythmias inducible with programmed electrical stimulation (18-23). These models seem most appropriate for investigating the mechanism of action of known antiarrhythmic agents and for predicting efficacy of new antiarrhythmic agents. Although most of these chronic infarct animal models do not have spontaneous tachyarrhythmias, the ability to reliably and reproducibly reinitiate ventricular tachyarrhythmias with appropriate programmed electrical stimulation allows these models to be exceptionally useful and even permits a given animal to serve as its own control.

Our laboratory has developed an occlusion-reperfusion canine model in which we occlude the anterior descending coronary artery just proximal or distal to the first large diagonal branch using a two-stage Harris procedure, followed two hours later by the release of the occlusion (19). In animals with extensive collaterals or anastomosing vessels we also ligate permanently at least two or three of the more prominent anastemosing epicardial vessels just at the cardiac apex. This procedure results in dogs with heterogeneous mottled infarctions with interspersing of normal and abnormal tissue. While these dogs do not develop spontaneous ventricular tachyarrhythmias it is possible using programmed electrical stimulation to initiate ventricular tachycardia and/or fibrillation in the majority of the animals operated on. The ability of programmed stimulation to induce a sustained ventricular tachycardia is still present two years after the initial occlusion-reperfusion surgical procedure (unpub-

lished observation). These animals can be investigated acutely in order to obtain detailed electrophysiological data at multiple sites including strength-interval curves, conduction times and refractoriness. It is also possible to study these animals with chronically implanted electrodes in the unanesthetized state and to use each animal as its own control over a prolonged period of investigation.

Despite the major advancement that the development of these chronic canine arrhythmia models have provided for evaluation of new antiarrhythmic agents, there still are numerous limitations. The metabolism of a drug can differ in the canine versus man. Even the evaluation of potential metabolites with antiarrhythmic action in the dog may not be a good predictor of antiarrhythmic efficacy. It is rewarding however that many of the antiarrhythmic agents that have been shown to be effective in man are effective in this chronic canine infarct model (23). The fact that the canine chronic infarct model is not one in which spontaneous sudden death occurs also points out that there must be differences between the canine model and man. Additional experiments on exercising animals and/or alterations of autonomic tone may show that chronic canine models do develop spontaneous arrhythmias.

The fact that the initiation of arrhythmias in these animals can be accomplished utilizing chronically implanted electrodes should permit the evaluation of antiarrhythmic drugs such as amidiarone which requires a considerable period of time before its total antiarrhythmic efficacy is developed. Also, since some of these animals will reliably exhibit ventricular fibrillation with programmed electrical stimulation it is possible to study antifibrillatory drugs in the model. This can provide support for the recent concepts that antiarrhythmic agents may not eliminate all ectopic activity but nevertheless decrease the incidence of sudden death. This question is an important one and one in which these chronic canine infarction models can certainly play a role. In addition, since in man many other complicating chronic diseases are often present besides myocardial infarction, these chronic canine models should prove valuable in evaluating interactions with hypo and hyperkalemia, drug interaction (i.e. digitalis) , left ventricular dysfunction and other factors associated with chronic disease states in man.

The recent demonstration by Myerburg that chronic infarction in cats produced by multiple ligations of distal coronary arteries can result in

had undergone shock conditioning as compared with a non-stressful environment where they were relaxed. The precise mechanisms by which psychological stress disrupts the electrical stability of the heart thereby facilitating the development of ventricular fibrillation is not understood. Undoubtedly, many different mechanisms are involved. The amount of circulating catecholamines as well as the epinephrine/norepinephrine ratio are altered and vagal tone is diminished. Although psychological stress is definitely involved in ventricular arrhythmias, the complex behavioral adaptations associated with different environments and the inherent variability makes it difficult to develop a standardized animal model to evaluate these psychological effects.

Another way that the cardiovascular effects of the autonomic nervous system are often studied is by electrical stimulation of the stellate ganglia. Although this provides valuable information, it does have limitations since simultaneous activation of all neural fibers in the stellate ganglia is an unlikely physiologic event. Another method for analyzing the effects of the sympathetic nervous system is by ablation of selective nerves. Using either stimulation or ablation it still is difficult to determine the direct effects of the sympathetic nervous system on the electrophysiological properties of cardiac fibers especially since the sympathetic system also affects cardiac rate, coronary circulation, contractility and blood flow (24).

The role of the parasympathetic nervous system in arrhythmogenesis and cardiac death is still controversial. Verrier and Lown have provided evidence that the protective effects of increased vagal activity is primarily indirect due to its opposition to the arrhythmogenic influence of the enhanced adrenergic activity. (10,24) Undoubtedly, a major vagal effect on cardiac arrhythmogenesis is that decrease in heart rate helps to preserve under perfused tissue from impending ischemia. It also has been shown that acetylcholine has very little action on normal Purkinje fibers but does depress automaticity in diseased Purkinje fibers. The delicate balance between alteration in vagal and sympathetic tone at the time of myocardial infarction almost certainly plays a role in the suppression or development of lethal arrhythmias.

In addition to their beneficial effects, cardioactive drugs oftentimes can also produce arrhythmias. Three drugs which are arrhythmogenic and have been utilized in animals to evaluate antiarrhythmic agents are

digitalis, aconitine, and catecholamines. Digitalis is probably the most commonly used drug to establish an arrhythmia model for testing antiarrhythmic agents. Two major problems with drug models are that the arrhythmias are primarily due to altered automaticity and that it is difficult to reliably attain a steady state level of toxicity (11). Neverthess, drug models have received reasonably wide scale use in the pharmaceutical industry for studying new antiarrhythmic agents despite difficulties in interpreting results.

Ventricular fibrillation is one of the primary causes of early sudden death after myocardial infarction (10). It is associated with electrical instability of the ventricles. Fibrillation is most often initiated by a rapid ventricular tachyarrhythmia or a premature ventricular contraction falling within the vulnerable phase of the preceding beat (R on T phenomenon). In 1940 Wiggers and Wegria discovered that an appropriately timed electrical impulse of sufficient strength delivered to the ventricles in late systole could induce ventricular fibrillation (28). Since these initial studies, numerous variations of that technique have been utilized to evaluate the vulnerability of the ventricle to fibrillation. All techniques have in common the fact that the relatively high currents (15-40 mA) must be delivered during the vulnerable period of a single cardiac cycle, or if lesser intensity currents are used, they must be delivered during the vulnerable periods spanning multiple sequential cardiac cycles. The technique of Wigger and Wegria utilized a single 10-msec pulse of increasing current to scan late systole. This is a time-consuming technique, since several time intervals during repolarization have to be tested at each intensity of current until fibrillation is finally induced. This nevertheless is still a frequently used technique. To reduce the time involved in making a single measurement of ventricular fibrillation threshold, Han employed a train of current pulses that scanned the T wave of the electrocardiogram (29). With this technique, it was necessary only to increase the intensity of the train of pulses in a step-wise fashion until fibrillation ensued. This is a commonly used and reasonably reproducible technique. Sugimato et al used constant current 60 Hz pulses of twice the diastolic threshold intensity passed continuously through the ventricular myocardium until the successively evoked premature beats deteriorated to fibrillation (30). The index of ventricular fibrillation using this method was not the

intensity of the current but the length of time the current had to be passed until the tachycardia produces fibrillation. Variations of the ventricular fibrillation threshold technique have been developed by other labs including passing increasing intensity current discharges across the chest wall to induce fibrillation. Other workers have used the amount of current required to induce nonsustained tachycardia as an indication of ventricular vulnerability (31).

The advantage of the ventricular fibrillation threshold technique is that it allows one to study the influence of single factors on ventricular vulnerability in a controlled system free of many of the variables associated with fibrillation in the intact animal setting. Thus interpretation of the data from the VFT experiments as they relate to the complex clinical setting must be made with care so as not to extend beyond the limits of the data of the experiment. Ventricular fibrillation threshold studies performed on patients undergoing open heart surgery indicate that the VFT threshold technique does give an indication of perturbations likely to result in increased electrical stability of the ventricles and decreased likelihood of ventricular fibrillation occurring (32).

Animal arrhythmia models have been useful not only to probe and demonstrate new mechanisms of arrhythmogenesis but also to analyze the effectiveness and mechanism of antiarrhythmic efficacy. Unfortunately no single model can predict the effectiveness of a cardioactive agent in man. However, by using a series of different animal models including cellular electrophysiological models, acute and chronic myocardial infarct animal models, ventricular fibrillation threshold models as well as neural and drug arrhythmia models it is possible to identify new antiarrhythmic agents. In addition, animal models can also be utilized to evaluate new methodologies of programmed electrical pacing and implantable automatic defibrillators for antiarrhythmic therapy in man. Although we still have not developed the ideal animal model which stimulates ischemic heart disease in man, we nevertheless are making marked progress towards understanding our animal models and how they predict human disease. New animal models will undoubtedly play a major role in decreasing the present unacceptable high incidence of sudden cardiac death in man.

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APPLICATION OF PHARMACOLOGIC PRINCIPLES IN THE EVALUATION OF NEW ANTIARRHYTHMIC AGENTS

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One of the major goals of investigations of new drug therapy is the establishment of practical guidelines for patient management. Some drugs are found to have very wide margins between the dosages that produce desired effects and those causing adverse reactions. Developing guidelines for the use of such drugs is not likely to be a problem because interpatient pharmacologic variability is insignificant compared to the width of this therapeutic window. However, the therapeutic window is often very small for cardioactive drugs. Therefore, information on any factor which contributes to interindividual variability in response may be helpful in maximizing therapeutic effects while minimizing the risk of adverse reactions.

I. IN WHAT POPULATION SHOULD DATA BE GATHERED?

Current guidelines suggest that initial testing of antiarrhythmic drugs should be performed in normal individuals. However, in normal volunteers there is no logical endpoint to guide dosing except side effects and unnecessarily high dosages may be given. Likewise, such pharmacokinetic studies may evaluate dosages in a range that is higher or lower than that eventually found useful in patients with diseases. Normal volunteers are therefore exposed to risk without any conceivable benefit to the individual. Furthermore, kinetic information gathered in normal volunteers (most often young apparently healthy males) invariably differs from that observed in patients (Table 1, next page).

We advocate initial human studies in patients with stable cardiac rhythm disorders. By starting at low dosages and increasing slowly, the chances of observing a salutary effect are maximized and the chances of side effects minimized. This strategy has been successfully applied in early studies in man, using either single escalating doses (1) or slowly increasing oral dosage regimens (2,3). Patients for these studies are selected to have stable, high frequency

Table I. Antiarrhythmic Drug Elimination Half-Lives (mean of reported values)

	Normal Volunteers	Patients with Chronic Arrhythmias
Tocainide	11 hr	14 hr.
N-acetylprocainamide	6.5	10
Mexiletine	10.5	12.5
Aprindine	22	48
Flecainide	14	20.3

ventricular arrhythmias and starting dosages are purposely chosen to be at or below those likely to be ineffective. Information gathered in this population has often been found applicable to later therapy in similar patients and provides dose/concentration information which serves as a starting point in managing other patient groups (recurrent sustained ventricular tachyarrhythmias, acute myocardial infarction), in whom the physician may not have the luxury of prolonged placebo therapy, or of using ineffective dosages or drug withdrawal/rechallenge (Figure 1). As a corollary, extensive dose-response and time-concentration studies are generally much more difficult to carry out completely in these less stable patients, because changing hemodynamics, the presence of other disease states, multiple drug therapy and the sporadic nature of recurrent sustained ventricular tachyarrhythmias all confound interpretation of the data. It is also important to recognize that such patients are less likely to tolerate drug-induced hemodynamic or electrophysiologic alterations than the more stable group (4). Limited information gained during studies in such patients is of course invaluable in treating similar patients later. Newer approaches to pharmacokinetic modelling which involve analysis of one or two samples from each of a large number of patients may in the future allow greater extraction of useful information from studies in this more unstable group (5).

The question of which population to study in assessment of the influence of specific disease states such as renal or hepatic dysfunction on drug action remains unresolved. It is difficult to collect a series of patients with isolated renal or hepatic disease plus chronic ventricular ectopy, so a compromise must be made. In practice, data gathered during early disposition studies (e.g. fraction excreted unchanged in urine, fraction metabolized) provides rough guidelines for later

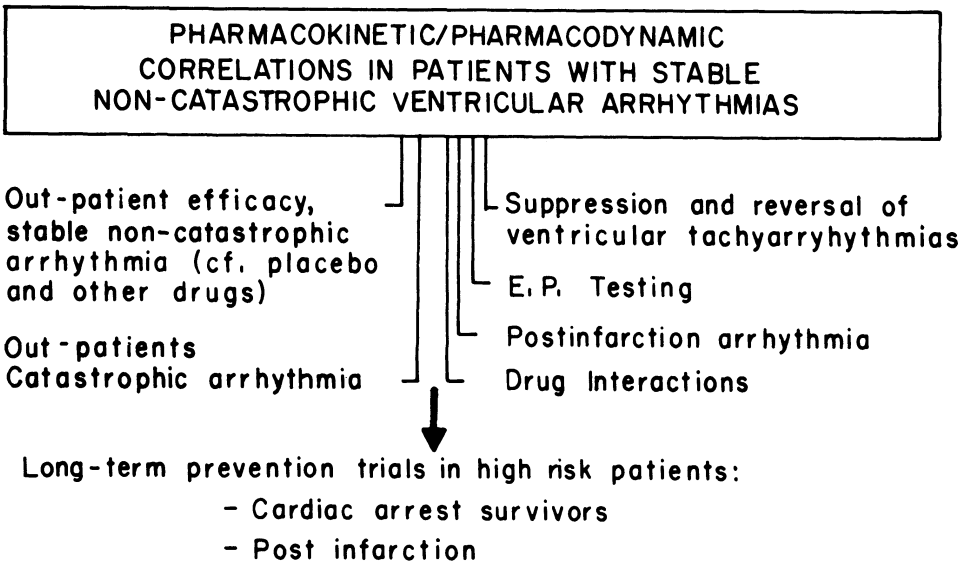

Figure 1: Sequence of investigations for the workup of a new anti-arrhythmic agent. Note that the first human studies are conducted in patients with arrhythmias.

therapy in patients with these conditions. Nevertheless, there is no substitute for slow dosage titration since unanticipated effects can certainly occur: anti-arrhythmic responses to extraordinarily low doses of procainamide in patients with renal failure (due to N-acetylprocainamide accumulation) remains the best example (6). Once safe dosages have been established, formal kinetic studies using these dosages in volunteers can be justified.

2. DATA TO BE COLLECTED

The production of an effect by a drug can be conceptually divided into two parts. The first, pharmacokinetics, describes the time course of drug concentrations in plasma and, in theory more often than in practice, in tissue. In this way, interindividual differences in this time course can be perceived and efforts made to minimize them. The second part of understanding drug action has been termed pharmacodynamics, and consists of the study of the relationship between drug concentration and the effect it produces. While studies involving drug administration to man almost always describe some drug effects, formal studies in this area have been uncommon perhaps because the methodology is not standardized. Nevertheless, greater knowledge of the range of effects produced by a given drug concentration (and eventually the mechanism for such differences) may help minimize interindividual variability in drug response. While it is conceptually and mathematically convenient to separate pharmacokinetics and pharmacodynamics, they are obviously linked. For instance, a pharmacokinetic variable, elimination half-life, only becomes a useful piece of information once pharmacodynamic data describing the relationship among drug efficacy, drug toxicity and plasma concentrations become available and are found to be linearly related.

2.1. Pharmacokinetic Studies. A number of well-defined pharmacokinetic variables can be derived from studies in man. In general two approaches are used: one involves modelling the body in terms of a series of "compartments", using various computer programs to fit raw time-concentration data to the mathematical form predicted by the modelling and then deriving useful parameters such as clearance or volumes of distribution from these "fitted" data. An alternative approach makes no assumptions about compartments but derives similar parameters. While it is tempting to assign certain anatomic areas to various compartments this is not generally justified. It is important to note that plasma concentrations during chronic therapy are usually either equal to or in equilibrium with those at whatever site is responsible for the final pharmacologic effects. Therefore, plasma concentrations can generally be regarded as useful guidelines to those at effector sites (with some exceptions as discussed below). An often-overlooked variable of which the investigator should be aware is imperfect plasma assay methods. Lack of specificity may lead to erroneous data, particularly if metabolites whose actions are not the same as that of parent drug are included (e.g. older quinidine assays

(7)). Chromatographic methods, in general, improve sensitivity and frequently can be modified to measure metabolites. Enzyme immunoassay (Emit^{R}) is far faster and more convenient but may be less sensitive and more expensive.

2.1.1. Absorption. Absorption depends largely on physical factors, such as tablet formulation (e.g. as with digoxin (8)), and can also be altered by concomitant drug therapy (e.g. antacids, bile acid sequestrants) or gastrointestinal pathology. Extent of absorption is usually assessed by measuring urinary and fecal recovery of a known administered radiolabelled dose. Sophisticated assay systems are not required and in fact are undesirable since recovery of parent drug and metabolites is needed. The label should be part of a metabolically stable molecular skeleton. Large fecal recoveries render interpretation of the studies more difficult unless it can be shown that enterohepatic recirculation has occurred.

For drugs with both rapid absorption and elimination, elimination is usually slower. However, slow release drug formulation can retard drug release in the gut to such an extent that absorption becomes the limiting step in drug disposition. In this way, slow release forms can be devised to decrease the required frequency of dosing. The traditional method of ensuring drug availability with a given formulation is to measure bioavailability. This is usually expressed as the total area under the time-concentration curve (AUC) as a fraction of a known standard, usually an equal intravenous dose (which is by definition 100% bioavailable). Decreased bioavailability can reflect a disturbance of absorption and is clinically most significant when it is variable (8) or low. For example, oral bretylium is only 23% bioavailable because of poor absorption (9); this probably reflects its chemical structure (quarternary ammonium) and obviously has implications for other quarternary compounds. However, decreased bioavailability of an oral dose of drug can also reflect pre-systemic metabolism. This most often takes place in the liver (although it can occur in the gut wall) and is a major determinant of disposition for drugs which are avidly metabolized by the liver. These include lidocaine (10), propranolol (11), and encainide (12). Lidocaine is well-absorbed but de-ethylated in the liver to metabolites which produce side effects (13); giving lower doses avoids side effects but fails to produce antiarrhythmic lidocaine plasma concentrations. Encainide is also dealkylated and the metabolite produced, O-demethyl encainide, is more potent (14,15) and more slowly eliminated (12) than parent drug. Routes of administration which avoid the first-pass effect will cause alterations in the ratio of metabolized to non-metabolized drug and so alter dosage regimens. These

include not only the intravenous route, but possibly also sublingual and intrarectal (16) administration as well as oral administration in patients with portosystemic shunting (17).

2.1.2. Distribution. In general, two processes, distribution and elimination, account for declining plasma drug concentrations. An occasional drug fails to exhibit any discrete early distribution phase and can be modelled as a single compartment. Since distribution is usually fairly rapid, it is often inapparent when drugs are given orally and the slower absorption and elimination processes dominate. Conversely, precipitous declines in plasma drug concentrations immediately following intravenous doses generally reflect rapid distribution into tissues rather than elimination. For drugs such as lidocaine whose effects are a function of plasma concentration, this drop can be accompanied by a rapid loss of efficacy, necessitating further doses to maintain effective plasma concentrations (18,19). Conversely, drugs whose actions depend in whole or in part on accumulation at sites outside plasma (bretylium (20), (?) amiodarone) may produce no immediate pharmacologic effect despite high initial plasma concentrations. Drugs whose plasma concentrations always closely correlate with cardiac activity are thought to exert their effects by rapidly interacting with sites on the surface of cardiac cells. On the other hand, a delay in onset of action could be due to slow uptake into a peripheral "compartment" (e.g. interior of cells) or slow interaction between drug and effector site.

The distribution process depends on physicochemical properties of the molecule, including extent of binding to plasma proteins and to tissue. For many drugs the free fraction in plasma is the pharmacologically active form; small changes in plasma protein binding of highly bound drugs may cause marked changes in the concentration of free drug. Similarly, monitoring total plasma drug concentrations as a guide to therapy is only justified if plasma protein binding is constant. However, binding of some drugs (e.g. disopyramide (21)) changes over the usual plasma concentration range and disease states can profoundly alter binding (e.g. free phenytoin, usually 10%, rises to 20% in renal disease (22)). For some drugs, tissue binding is a major determinant of activity (e.g. digoxin); for these agents, displacement from tissue can alter pharmacologic response (a putative mechanism to partially explain the digoxin-quinidine interaction (23)).

Pharmacokinetic analysis can yield various "volumes of distribution", which generally correspond to no physiologic space and which, because of protein binding, may exceed the total body volume several-fold (24). (Essentially, these are derived by dividing a given dose by an observed plasma concentration). The so-called

central volume of distribution (Vc) is an index for the way drug distributes immediately after an intravenous bolus and is obtained by dividing the dose by the back-extrapolated plasma concentration at time zero. Disease states which alter Vc (e.g. lidocaine Vc decreased by 50% in heart failure (25)) change the size of the bolus required to produce the same plasma concentration. Other volumes (Vd_{β}, Vd_{ss}) provide indices of total distribution ("central" plus "tissue") and may be better guides to changing dosages during chronic therapy.

2.1.3. Metabolism and Elimination. These processes are generally assumed to proceed at a rate which depends on the amount of drug present, i.e. "first-order" kinetics. It is a mathematical corollary to this assumption that the processes can then be described in terms of rate constants or, more commonly, half-lives ($t_{½}$ = natural logarithm of 2 divided by the rate constant). Most pharmacokinetic processes, including absorption and distribution as well as elimination, can be characterized in terms of half-life. Half-life is by definition, the time required for 50% of a process to be complete; two half-lives complete 75%; and so on (Table 2).

Table 2 - Relationship between half-life and extent of completion of a first-order process

number of half-lives elapsed	amount of drug excreted[1]
1	50%
2	75
3	87.5
4	93.8
5	96.9
6	98.4
7	99.2

[1] or accumulated to steady state, distributed, etc.

Four to five half-lives are sufficient for most processes (elimination, distribution) to be considered complete. Four to five elimination (accumulation) half-lives is also the time required for steady-state conditions (amount given = amount eliminated) to be achieved during chronic therapy. The assumption of first-order elimination is usually valid. However, for some drugs (phenytoin, aspirin, (?) propafenone, (?) lorcainide) metabolism and/or elimination can be saturated (26). Under these conditions, elimination becomes "zero order", i.e. independent of

concentration, and a certain mass is removed per unit time regardless of amount of drug present. Small increments in dose can then cause disportionate rises in plasma concentrations and increase the attendant risk for drug toxicity in this situation.

Half-life of elimination is not an index of the activity of the elimination process. This is more accurately assessed by clearance (which can be divided into renal clearance, non-renal (usually hepatic) clearance, etc), i.e. the amount of plasma completely cleared of drug per unit time. During intravenous therapy, steady-state plasma concentrations (Cpss) depend only on dose and clearance:

$$Cpss = \frac{\text{Dose (per unit time)}}{\text{Clearance}}$$

With oral therapy, the average concentration between doses is given by the above expression while the inter-dose "swings" are determined by elimination half-life and rapidity of absorption (absorption rate constant). The dosing interval in turn is constrained not only by the elimination half-life but also by the difference between plasma concentrations associated with efficacy and those producing toxicity (the therapeutic window). If this window is wide, infrequent dosing is feasible even with rapidly eliminated drugs, whereas if the window is narrower, dosing must be correspondingly more frequent (Figure 2).

Volume of distribution, elimination half-life and clearance are related in the following way:

$$t\,½ = \frac{Vdss}{Cl}$$

Therefore, in disease states producing proportionate decreases in both Vd_{ss} and Cl, elimination half-life (the time required to reach steady state) may be unaltered, while plasma concentrations will be raised. Heart failure has this effect on lidocaine kinetics (25) and quinidine produces a similar change in digoxin kinetics (27). The effects of other alterations are also predictable from the above relationship.

While metabolism generally inactivates drugs, formation of active metabolites has become increasingly recognized as a major determinant of net pharmacologic effect. This becomes most relevant to therapy when active metabolites are eliminated more slowly than parent drug, and so gradually accumulate. Obviously, generation of metabolites with pharmacologic activity confounds plasma

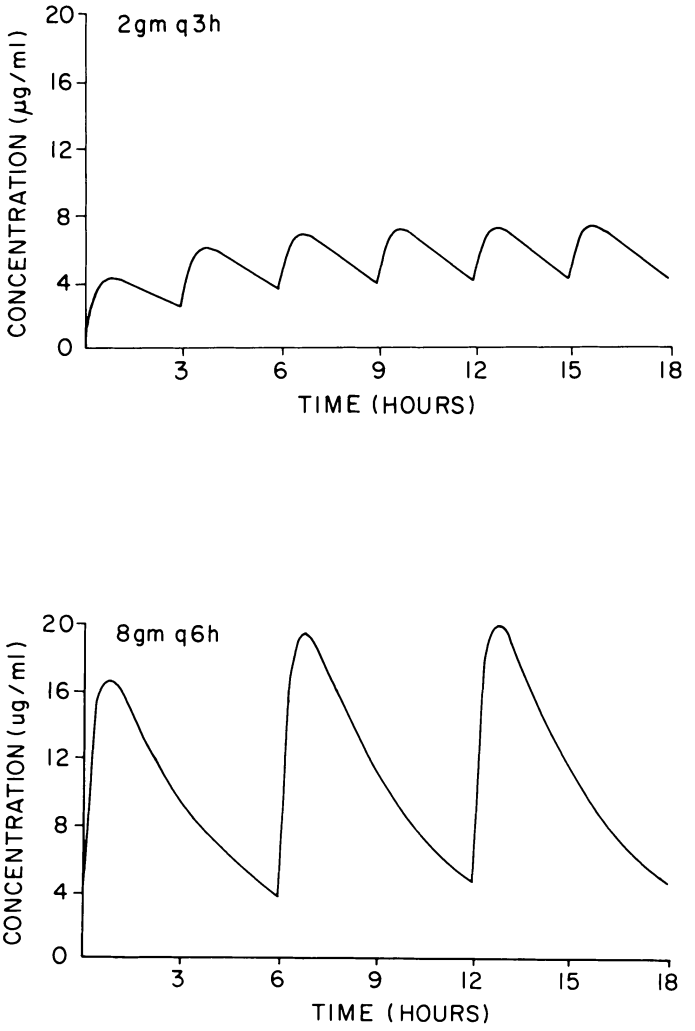

Figure 2: Relationship among the elimination half-life, the width of the therapeutic window and the frequency of dosing for a rapidly absorbed and eliminated drug (in this case procainamide). These computer simulations of plasma concentrations show that frequent dosing is required when the therapeutic window is narrow (4-8 µg/ml; top panel) to avoid excessively high or low values. If the therapeutic window were wider (e.g. 4-20 µg/ml; bottom panel), larger doses could be given less frequently. Since elimination half-life (139 minutes) is not changed, the time to reach steady-state conditions is the same (10-12 hours, see Table 2).

concentration-effect analyses and may cause unexpected efficacy or toxicity especially if dosages are changed before metabolite has accumulated to its steady state levels.

The best-studied example is N-acetylprocainamide, whose activity was first suggested by arrhythmia suppression in patients with renal failure receiving very small doses of procainamide (6). Despite strong circumstantial evidence, its antiarrhythmic activity in man could only be confirmed when it was administered to patients (3,28). Parent drug and metabolite can differ considerably in pharmacologic properties. For instance, N-acetylprocainamide appears to exert relatively less effect on conduction velocity than procainamide (29). In addition, while procainamide generally produces arrhythmia suppression at plasma concentrations over 4 μg/ml and side effects above 8 μg/ml, the corresponding range for N-acetylprocainamide is 9-19 μg/ml (3). Norlorcainide is also active and has been tested in man (30), while O-demethyl encainide and its metabolite 3-methoxy-O-demethyl encainide, are active in vitro and in animal models (14,15) but have not yet been tested in man. These metabolites in fact are probably responsible for most effects of encainide therapy in man (2,31). Quinidine (32), disopyramide (33), aprindine (34) and lidocaine (13) also have metabolites which are active in vitro or in animals but the contribution of such metabolites to net activity remains undetermined. Awareness of the existence of active metabolites, the ranges of their plasma concentrations associated with efficacy and toxicity and the time course of their accumulation are all required to avoid unanticipated drug toxicity.

Pharmacokinetic studies seek to characterize time-concentration data in a systematic way, thereby allowing insights into the mechanisms of drug action and disposition and allowing predictions of subsequent time-concentration relations. However, it is clear that these data alone are of limited clinical value and assume their greatest importance in patient care when linked to information on dosages and concentrations associated with therapeutic and toxic effects.

2.2. Pharmacodynamic Studies. An understanding of the relationship between drug dosage and effect forms the basis for all therapeutics. However mathematical characterization of this relationship has lagged far behind pharmacokinetic studies. The problem of effect depending on drug concentration at a site outside (and not

always in equilibrium with) plasma has been mentioned above. Even the mathematical form of the relationship between effect and plasma (or tissue) concentration (or log concentration) remains uncertain. For example, effects such as QRS prolongation can usually be considered a linear function of some concentration term, while other effects, such as suppression of ventricular ectopic depolarizations (VEDs), require more elaborate modelling (no concentration can produce more than 100% arrhythmia suppression (35)).

In order to characterize patient response to drugs, two endpoints, efficacy and toxicity, need to be defined. As already mentioned the difference between these two (either in terms of plasma concentration or dosage) is a major factor in patient management. Widely quoted therapeutic plasma concentration ranges should be considered merely guidelines to therapy and are no substitute for patient observation. The lower end of the therapeutic range is a concentration likely to be effective. This value in turn depends on a definition of efficacy. For example, in the course of tocainide therapy in a group of patients with recurrent non-sustained ventricular tachycardia (36), we found that 90% suppression of VT episodes could be obtained at plasma concentrations of 2.8-10.0 μg/ml (mean 6.0) while 90% VED suppression required 9.0-13.0 (mean 11.0). While this relationship between suppression of non-sustained complex arrhythmia and isolated VEDs generally holds true in patients with chronic rhythm disturbances, prevention of sustained VT is less predictable.

The upper end of the therapeutic range is also just an estimate of a concentration beyond which the chance of side effects rises faster than that of a beneficial effect. Some patients may still respond at high concentrations and not develop side effects (37). If anticipated side effects are mild, a higher value for this estimate is acceptable; if side effects are likely to be severe, a lower limit must be proposed. It is important also to remember that not all side effects are directly related to plasma concentrations; procainamide-induced lupus and quinidine-induced torsades de pointes are examples.

Other effects such as ECG interval prolongation should also be studied early during drug testing in man, both to provide guidelines for patient monitoring and to gain insight into potential mechanisms for drug action. As outlined below, the relationship between plasma concentrations and effects can provide an important clue to the existence of active metabolites.

3. IMPORTANCE OF THE DATA COLLECTED.

Acquisition of the pharmacokinetic and pharmacodynamic information outlined above is an ongoing process which is incomplete for all drugs. Nevertheless, certain measures should be obtained very early in the course of investigations in man since they are important in early detection of potential problems in therapy (Table 3).

TABLE 3 - PROPOSED SEQUENCE OF PHARMACOKINETIC STUDIES DURING THE WORKUP OF A NEW ANTIARRHYTHMIC AGENT.

I. INITIAL EVALUATION

A. Assay Development
B. Basic Kinetic Studies

- ABSORPTION
  - Bioavailability
- DISTRIBUTION
  - Protein Binding
- ELIMINATION
  - Clearance
    - Presystemic
    - Renal
    - Total
  - Clearance vs. Dose
  - Half-life

C. Plasma Concentration/Effect Relationships

II. COMPREHENSIVE EVALUATION

A. IV/Oral Studies
B. Single Dose/Steady State Comparison
C. Disease States

- RENAL INSUFFICIENCY
- HEPATIC INSUFFICIENCY
- CONGESTIVE HEART FAILURE

D. Evaluation of Activity of Metabolites

Early development of sensitive and specific assay methods are obviously important to the conduct of all these studies. Formal evaluation of bioavailability (oral vs intravenous) is necessary, but even in its absence, marked interpatient variability in area under the time-concentration curve after identical oral doses strongly suggests variable bioavailability (2). In such a case, either absorption is impaired or a significant first-pass effect is present. The implication of poor absorption is clear and obviously should be detected early in human studies. Similarly, if a high first-pass effect is present, dosing recommendations for oral and intravenous therapy may be quite different. If clearance is constant the relationship between dose and area under the curve should be linear (clearance = Dose/AUC). If clearance falls with increasing doses, saturable kinetics, with their implications for dosage changes, may be present. Comparison of concentration and effect data after single and multiple doses is also important to detect unanticipated drug accumulation or effects which might suggest the presence of active metabolites. Single dose kinetic data also provides elimination half-life measurements which, along with efficacy/toxicity data, may give a clue to the required frequency of dosing (assuming active metabolites are not a major consideration).

The other key pieces of information which should be sought from the first patients are the dosage and plasma concentrations associated with efficacy and toxicity. The width of this window is ultimately the most important determinant of how well-tolerated therapy is likely to be. A scatter in interindividual minimal effective plasma concentrations may have several important implications. First, active metabolite(s) may be present; lack of such a scatter does not imply the opposite since such metabolites may accumulate only in certain settings (e.g. N-acetylprocainamide in renal failure). Alternatively, concentrations at some peripheral effector site may be more important than those in plasma. A third possibility to be considered is a non-specific assay system.

Studies such as those outlined above can be completed in a relatively small number of patients. Larger efficacy studies, based on dose or plasma concentration guidelines can then be undertaken. Complete characterization of kinetic variables in patients with various disease states (heart failure, liver disease, acute myocardial infarction, etc) can then be obtained and compared to data obtained in the more stable group. An approach which we have found useful particularly with drugs such as propranolol (11) and encainide (12) which undergo extensive presystemic clearance is illustrated in Figure 3. It involves the simultaneous

administration of an oral dose and a radiolabelled tracer intravenous dose. Measurements related to the intravenous route (systemic clearance, Vc) and to the oral route (bioavailability, hepatic extraction) are obtained simultaneously. In this way, intraindividual variability over time is factored out and full data sets can be obtained at multiple points in time (e.g. first dose vs steady state). Pharmacokinetic data also allow insights into the mechanisms of drug interactions (38) and design of intravenous dosing regimens (39) likely to be safe and effective.

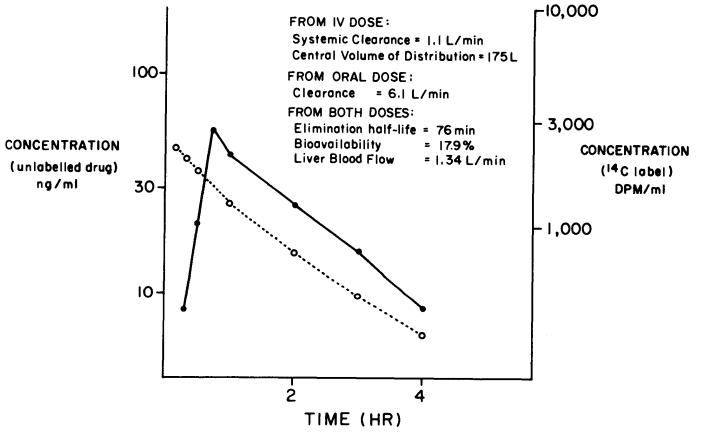

Figure 3: Total plasma encainide (solid symbols; left ordinate) and radioactive encainide (open symbols; right ordinate) following administration of a usual oral dose (50 mg) and a simultaneous radiolabelled tracer intravenous dose. Pharmacokinetic values calculated from these data are shown. Using this approach, parameters can be collected again during chronic drug administration, metabolite formation and accumulation can be characterized, and the influence of drug interactions and disease states on drug disposition assessed.

It is our contention that active metabolites, if they appear to be present, should be tested early in patients. In this way, activity can be confirmed, pharmacokinetics can be characterized, and concentration ranges likely to be relevant during therapy with parent drug can be established.

Until recently it was not routine to measure plasma concentrations in the course of drug development. It is our hope that the series of considerations outlined above becomes a routine part of early drug development so safe and effective therapy can then be undertaken in large numbers of patients.

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CHARACTERIZATION OF ANTIARRHYTHMIC DRUGS

B.F. HOFFMAN, M.D.

To characterize an antiarrhythmic drug, measurements need be made of its effects on the electrical activity of the heart and also on the membrane potentials of single cardiac fibers. The former measurements are essential to identify and quantify the effects of the drugs on electrical activity whereas the latter are needed to obtain some indication of the mechanisms for these effects.

Effects on Cardiac Electrical Activity

Measurements of electrical activity of the intact heart should include data describing effects on impulse generation in the sinus node, sinoatrial conduction, conduction through the AV node, conduction in the His Purkinje system and conduction in atrial and ventricular muscle. In general, it is least informative to make these measurements on the hearts of small mammals like rats or guinea pigs, in which the heart rate is extremely rapid. This is so because the actions of most classes of antiarrhythmic drugs, both those that block fast inward (sodium) and slow inward (calcium) channels show use dependence, i.e., the intensity of effect is a function of the repetition rate of the action potentials (1). Also, for some drugs, the intensity of use-dependent depression of electrical activity may depend on the action potential duration. A reasonable compromise is to use the in situ canine heart.

Evaluation of drug effects on impulse generation in the sinus node should include measurements made after selective blockade of beta-1 adrenergic and muscarinic receptors.

This is particularly important for drugs that may be slow channel blockers because (a) norepinephrine antagonizes the effect of such drugs on sinus node fibers and (b) such drugs often liberate catecholamines reflexly and thus mask their depressant effect on sinus impulse generation. Since it is possible to record sinus node activity through an extracellular unipolar lead, and directly evaluate changes in sinoatrial conduction time, this technique should be used routinely (2).

For an evaluation of drug effects on AV conduction, studies should be made with the atria paced at both slow and quite rapid rates because drug induced impairment of AV transmission is much more likely to be demonstrated during an atrial tachycardia. Standard techniques to record His bundle electrograms through an electrode catheter can be employed and AV nodal conduction evaluated from changes in the A-H interval; conduction in the His Purkinje system can be evaluated simultaneously from changes in the H-V interval. Since, as mentioned above, the intensity of effect of the local anesthetic antiarrhythmics shows use-dependence effects on H-V intervals and the QRS complex must be made over a wide range of heart rates to estimate the intensity of drug action for any drug concentration. Drug effects on conduction in ventricular muscle can be assessed from changes in the QRS complex, once direct depressant effects on the specialized conducting system have been evaluated from the His electrograms. Effects on action potential duration in the ventricle can be estimated from changes in the Q-T interval but direct measurements of refractoriness are desirable. For these, it is preferable to use a unipolar cathodal electrode as shown many years ago, and to make measurements at several different paced heart rates. Most, if not all, local anesthetic type antiarrhythmic drugs have an action that can be described as causing a shift in the steady state inactivation curve for fast inward channels to more negative transmembrane potentials.

Also, the intensity of block of fast inward channels is a steep function of transmembrane potential, growing more complete at reduced transmembrane resting potentials. Because of these effects, local anesthetic antiarrhythmic drug action is strongly dependent on the extracellular potassium concentration. A decrease in serum potassium by 1-millemole from the usual value may greatly decrease the intensity of drug action and an increase by as little as 2-3 millemoles from the usual value may greatly potentiate drug effect. For these reasons it is essential to make measurements when serum potassium concentration is known and also after the serum potassium concentration has been increased by 3-4 mM/liter. These measurements are made not only to control for changes in serum potassium, such as those that might occur as a result of renal insufficiency but rather to permit an estimate of the increase in intensity of drug effect that might result from extremely rapid rhythms or regional ischemia. In both conditions extracellular K^+ concentration may rise quite markedly.

Although the relevance of fibrillation thresholds to clinical fibrillation is uncertain it probably is worthwhile determining the effects of a new drug on both the fibrillation threshold and the current required for defibrillation. The importance of the latter measurement needs no emphasis. Instead of fibrillation thresholds one can use the threshold for multiple responses (3).

Effects on Experimentally Induced Arrhythmias

Tests against digitalis-induced ventricular arrhythmias and ventricular arrhythmias occurring 24 hours after coronary artery ligation in the canine heart clearly are useful because of the vast experience with these causes of ventricular arrhythmia in the canine heart. Tests also should be conducted at longer intervals after infarction (4) to evaluate a model in some ways comparable to the human heart that develops reentrant ventricular arrhythmias weeks or months after infarction. Data from several laboratories indicate that temporary coronary occlusion followed by

reperfusion produces in the canine heart an infarct that is susceptible to induction of reentrant excitation by overdrive or premature stimulation and that seems to discriminate among antiarrhythmic drugs. Tests also should be made against atrial arrhythmias and several models of reentrant atrial tachycardia in the canine heart have been described (5,6). Arrhythmias induced by focal application of aconitine or by barium, cesium or other chemicals do not permit easy evaluation and interpretation of drug effects. Arrhythmias induced in the hearts of small animals by a variety of means may be quite misleading. For example, the persistance of atrial fibrillation and ventricular fibrillation is a predictable function of heart size and so effects demonstrated in the mouse or rat heart might have no relevance to the much larger human heart.

If possible, outcomes of drug action should be evaluated in a different sense. Obviously it is important to determine whether or not a drug increases the likelihood that fibrillation will terminate spontaneously. In this case again, the use of a suitably large heart is essential. Measurement can be made easily on a supported heart or during cardiopulmonary bypass, with fibrillation induced by electric current. Perhaps more important, studies should be directed toward evaluating any effect of the antiarrhythmic drug on the likelihood that a rapid ventricular rhythm will degenerate into fibrillation. Also, in appropriate models with infarcts, studies should evaluate the possibility that the heart may be made susceptible to arrhythmias that were not likely before drug administration.

Studies on Cellular Electrophysiology

For any new antiarrhythmic drug, measurement should be made of its effects on the transmembrane potentials of isolated preparations of cardiac tissue. Since measurements can be made both for normal preparations and preparations in which arrhythmogenic mechanisms are operative, the studies provide reasonable clues to the mechanisms for antiarrhythmic action and also indicate the types of arrhythmias likely to be influenced by the drug at usual concentrations. Bundles of

Purkinje fibers are employed most often because of their general suitability to experiments with intracellular microelectrodes. However, some experiments also should employ atrial and ventricular muscle fibers since these may be involved in arrhythmogenesis and often will show quantitative differences in terms of intensity of drug effect. Under ideal conditions, voltage-clamp techniques should be used to characterize the basis for drug induced changes in the transmembrane potentials; but a reasonable amount of information can be obtained from the transmembrane potential record itself. Whenever possible, measurements should be made both under control conditions and after induction of specific arrhythmogenic mechanisms. A variety of methods is available for the induction of early and delayed afterdepolarizations, abnormal automaticity and reentry and reflection. Also, several methods can be used to induce slow response action potentials and test drug effects on the membrane potential changes caused by slow inward current. The use of voltage clamp techniques to measure drug induced changes in membrane ionic currents often is difficult and the interpretation of the data may depend on a number of assumptions. It seems likely that this method will be replaced in the near future by the use of the patch-clamp technique to directly record current in single ionic channels and its modification by drug action.

For standard studies, measurement should be made on drug effects on the resting potential, amplitude and rate of rise of the action potential, action potential duration, plateau voltage, time course of repolarization and phase 4 depolarization. Block of current in fast inward (sodium) channels can be evaluated from changes in the maximum rate of rise of the action potential upstroke $\dot{V}_{max}$, even though changes in this variable are not linearly related to changes in peak sodium current. Because most local anesthetic antiarrhythmic drugs demonstrate both tonic and use-dependent block, measurements of drug effect should be made at several different rates of stimulation. Also, the time course of development and decay of use-dependent block should be

quantified by suitable stimulus sequences. Effects of changes in resting potential on the intensity of block can be evaluated by making serial changes in extracellular K^+ concentration. Data describing drug effects on the recovery of responsiveness can be obtained by stimulating at different times during phase 3 and phase 4.

An estimate of drug effect on slow inward current often can be made from measurement of changes in plateau voltage or studies on slow response action potentials. Typically, these are induced by superfusing the tissue with a high potassium concentration and catecholamine. As mentioned above, several different models for specific arrhythmogenic mechanisms are available. Delayed afterdepolarizations can be induced quite routinely by superfusion of tissues with a toxic concentration of digitalis glycosides; alternatively an elevated extracellular calcium concentration and catecholamines can be employed. Abnormal automaticity, i.e., phase 4 depolarization and automatic rhythms, can be induced routinely by superfusion of canine Purkinje fibers with solutions containing a low concentration of barium (.025 to .1 mM) or less effectively by current clamp that prevents full repolarization. A reproducible technique to produce reflected rhythms through the use of a sucrose gap has been described (7) and several models of reentrant rhythms also are available. Perhaps the simplest is the leading circle reentry that can be induced in isolated rabbit atrial tissue (8).

Hemodynamic Effects

The overall goals of these measurements are to obtain some indication of drug effects on the capacity of the left ventricle to develop tension and shorten against a load and effects of the drug on the resistance and capacitance of the systemic and pulmonary circulations. If effects are observed, it is important to determine the extent to which they result from direct actions of the drug and the extent to which they result from drug-induced alterations in other regulators of the circulation. Finally, it is important to

determine whether the magnitude of any depressant effect on the circulation depends critically on reflex or other mechanisms that compensate for the primary effect of the drug. Since antiarrhythmic drugs usually are given to patients with abnormal hearts, some attempt should be made to assess drug effects of hearts that have lost their normal capacity to compensate for negative inotropic interventions.

An initial set of measurements should include systemic arterial pressure, systemic flow, left ventricular pressure and left ventricular size and shortening velocity. The latter two measurements can be made by attaching ultrasonic gauges to suitable locations on the heart. Measurements should be made at several paced heart rates before and after beta-adrenergic blockade. An isolated supported heart permits more meaningful evaluation of drug effects since both preload and afterload can be controlled. Measurements of effects on peripheral resistance can best be made using an isolated vascular segment perfused from a pulsatile pump. Evaluation should include studies on direct and indirect effects on vascular tone and modification of the actions of the autonomic nervous system. Studies on the coronary circulation probably should employ microspheres to quantify redistribution as well as changes in total flow. Obviously for these measurements ventricular mechanics must be controlled.

Schemes for Classification

In general, currently available classifications are not very helpful since the variables identified in the classification often do not describe unique effects on cardiac electrical activity. For example, a drug that prolonged refractoriness by delaying repolarization might exert effects similar to another drug that caused use-dependent block of fast channels and had an appropriate time constant for the disappearance of use-dependent block. When more has been learned about the nature of drug interaction with specific ion channels through the use of the patch-clamp, a meaningful classification should be possible. Until that data is available, it would

be useful to at least include a description of the kinetics of use dependent block for drugs that interact with either fast inward or slow inward channels.

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Dr. Ehrreich: Perhaps I could start by making a few remarks that might be helpful. There appear to be three reasons that I can see based on past experience why investigators in industry want to perform early studies of these drugs in animal models. The three reasons are firstly, to convince management that a drug has enough potential to justify toxicologic testing, a finite resource in which only a few drugs can be tested over time. Secondly, to convince a potential outside investigator that the drug is worthy of his/her attention. Finally, and last but not least, to convince the Food and Drug Administration of the merits of the drug. Let me just take the last one first. The FDA has no required laboratory experiments for antiarrhythmic drugs or most of the other drugs. What people look for is evidence that the drug has demonstratable pharmacologic activity in one or more animal models and that the drug has a fair margin between dosages with this activity and those which are toxic. Of course the toxicity studies are absolutely required. So if you have data from 5 models or 50 models, it doesn't matter. I think that is an important point. We recently had a meeting in Chicago on cardiotonic drugs and Dr. Leon Goldberg was a proponent of getting drugs into man as soon as possible within reason. I think this is exactly what I am trying to suggest. Industrial management should realize that you don't always need a 5 foot submission for approval to go into clinical studies.

Dr. Woosley: I think you have made a very good point. Many pharmaceutical companies feel that these models might provide evidence for relative potency by comparison to the standard antiarrhythmics providing guidelines for the early dosing for these agents. In that respect, Dr. Winkle, have you found animal data very helpful in selecting initial dosages for evaluation of antiarrhythmic drugs in early phase I-II trials?

Dr. Winkle: I certainly think it is not a perfect correlation. There is a reasonable degree of correlation especially between effective plasma concentration in animals and what we eventually see required in man, but it is not a 1:1 correlation by any means.

Dr. Woosley: Dr. Ehrreich at the F.D.A., is there any consideration in the early animal studies, of possible differences in the metabolic pathways that may exist compared to man.

Dr. Ehrreich: Certainly, the problem generally is to reconcile potential differences in metabolic pathways between man and animals. What might occur in rat, or rabbit, or dog or monkey may not necessarily occur in man, but the evidence that there is an active or potentially toxic metabolite is important to know. Likewise it is important for the pharmaceutical firm to know so that they can determine this at an early stage and decide how they wish to proceed. It may turn out that the active metabolite is indeed the drug to test and that is of course management's decision at that point. These considerations are definitely made.

Dr. Moore: One thing that has never been a problem with animal models is to identify an agent that has efficacy as an antiarrhythmic agent. That is never a problem. I think that perhaps one of the major roles that animal models play is as Dr. Ehrreich has already said, is in determination of potential dosages to be studied, dosing. However, another major role they can play is in identifying potential side effects. If one goes rapidly to man with a new agent, and runs into a problem of toxicity early on in man, it is likely to eliminate that agent from further testing. . The more information you have on that agent before you take it to man, the better. For example, if one has an agent which enhance AV conduction, and you happen to give it to a patient with atrial fibrillation, it may actually enhance the ventricular response rate leading to an adverse clinical response. All one has to have in

man is a few similar potential catastrophes, and it could kill what could potentially be a superb drug. I think that looking at a number of different animal models could give you a great deal of information. For example, as Brian Hoffman has already asked, is it harder to defibrillate a patient who has been given an agent? This might be predicted from animal studies.If one has data from a sufficient number of animal studies, one might save a potentially valuable agent and to the contrary one might be mislead to exclude a good drug from further testing.

Dr. Hoffman: I do think that downstream attitudes strongly bias upstream behavior. For example, suppose, in a particular laboratory, you find that when you do very careful electrophysiologic evaluation in a particular set of patients, 15% don't respond to any of the drugs that you use. And then suppose that you had a drug that would be quite efficacious in that 15% of people. If you study the drug in the usual way, taking folks with ventricular arrhythmias and doing nice placebo versus drug crossover studies, you would inhibit ventricular arrhythmias only in 15% of this very large, totally random population. I don't think the drug would probably get very far. Clinical evaluation of a drug satisfies everybody when a drug for unspecified ventricular arrhythmias works in a large proportion of patients without toxicity. Having such a narrow viewpoint, we eliminate the possibility of finding drugs that will work for less common arrhythmias. For example automatic supraventricular arrhythmias which for the most part don't respond to drugs. The system is interactive both in terms of forward and backward flow of influences and I think that has to be appreciated so that the development process can be improved. I am not saying this with the intent of criticism, I think it is the nature of the system and I think we ought to accept it.

Dr. Woosley: This discussion brings to mind the situation with a number of antiarrhythmic drugs that have been developed recently, eg. meobentine and clofilium. The developers have decided that, even if the drugs don't work in patients with stable PVC's, they will still go to a clinical application that may be more similar to the results from the animal model, e.g. electrically induced arrhythmias or ventricular fibrillation in the emergency room. This is based on the supposition that this class of compounds, often called the quaternary ammonium compounds or related agents, may have an antifibrillatory action separate from an antiarrhythmic action. Perhaps Dr. Hoffman or Ruskin would comment on the potential logic in this or whether we are putting too much credence in on our animal data.

Dr. Hoffman: I think it would be very desirable if one could identify drugs that either prevent fibrillation or caused spontaneous termination of fibrillation. In animal models, I think one can evaluate both those possible effects really precisely and accurately. I am not sure for humans, exactly how you would go about testing the same end points. It is tough and I wonder what you are going to provide the F.D.A. that will convince them for this class of drug.

Dr. Ruskin: I think that it comes down to the question of, what is pathophysiology of what we are trying to treat. Much of my enthusiasm for animal models relates not only to the ability in this setting to look at specific drug effects but more importantly to the ability to get at the underlying pathophysiology of the arrhythmias. We still don't know with any precision exactly what causes sudden death in each subgroup of patients at risk. We know that sustained ventricular tachycardia is a problem in a subgroup and I think you could use an appropriate animal model to learn more about the pathophysiology and examine drug efficacy for that arrhythmia. Also, death from of ventricular fibrillation may be related to an acute

ischemic event and a different phenomenon from the causes of sustained ventricular tachycardia. The pathophysiology is different and the drugs that we need to use in that situation may be quite different. Therefore, I don't think we have a perfect situation for testing of any of these cases and we won't until we have much more information about the precise pathophysiology of the specific arrhythmias that we are trying to prevent.

Dr. Woosley: Perhaps what sets ventricular arrhythmias apart from congestive heart failure with respect to Dr. Goldberg's recommendation, is that the pathophysiology of congestive heart failure is probably fairly homogeneous. Therefore you may not need a lot of studies in animal models to characterize a pharmacologic action. However, for a heterogeneous group of arrhythmias it may be very good to have as much information as possible from the animal models.

Dr. Ehrreich: Yes Ray, I am not suggesting that one shouldn't have animal models and of course the studies in animal models by industry are a major source of information and progress. However, I am saying that there are no specific requirements to have a certain number of studies performed and I think people thought there were; but there aren't. That is the only point I am making.

Dr. Winkle: I think that if we are going to learn from the animal models,we should continue a trend of the last few years that I feel has been appropriate. That is, towards using models in animals that are much more similar to what we have been using in man. I think that some of the old models that much of the pharmaceutical industry uses to screen drugs (chloroform arrhythmic induction perhaps aconitine atrial fibrillation induction) ought to be reconsidered, because I think there are many better and more relevant models now.

Dr. Wilson: A question for any of the panel members, but maybe Dr. Winkle, if I were to come along with a new animal antiarrhythmic drug and an investigational brochure for you, which of the pre-clinical animal models would you as a potential middle to late phase I investigator most like to see.

Dr. Winkle: My primary concern is to use the information to make some assessment of the drug's safety before giving it to patients. The types of safety considerations that I can relate to best would be studies evaluating the effects of the drug on the cardiac conduction system. Is the drug likely to produce block in the AV node, block in the His-Purkinje system? If I see that a drug that has potent effects on the His-Purkinje system, I would want to keep patients with bundle branch block out of the early studies, etc, etc. As has been said, there are so many models of efficacy, as long as there are some data to suggest that it has antiarrhythmic properties, I really am much more concerned about knowing information from models that will help me use it safely in the first patients. This might prevent the early catastrophes mentioned by Dr. Moore.

Dr. Woosley: Perhaps also information from hemodynamic studies?

Dr. Winkle: Yes, also hemodynamic studies; we haven't talked about that, but I consider those are very important for the same reasons.

Dr. Morganroth: Ray, on that line and taking it one step further, you touched on this in your talk. Do you think normal volunteer studies have a role for looking at initial safety or should those traditional type studies be abandoned for the chronic stable PVC patient population? I would like comments from the panel also on that.

Dr. Woosley: I am glad you brought that up. I think studies in normal volunteers in this area are dangerous, useless, and a waste of resources. Maybe the panel would like to address the question. Does anyone disagree? I

am glad, that we all agree. Although I think most people in industry agree, although there are some phase I pharmacokinetic and toxicity studies being done in normal volunteers.

I would like to ask one more question. Is a drug that causes parallel changes in refractoriness and action potential duration, but no change in the ERP to MAP, APD ratio of possible benefit clinically? Is that a bad effect to have in a drug?

Dr. Hoffman: That is the only thing it does?

Dr. Woosley: Yes.

Dr. Hoffman: Well then it is equivalent to decreasing basic heart rate, so I would say for an arrhythmia where a decrease in heart rate would be antiarrhythmic, then this drug might work. I don't know many arrhythmias are like that, but there might be some.

HOW SHOULD VENTRICULAR ARRHYTHMIAS BE CLASSIFIED AND WHICH PATIENTS SHOULD BE TREATED?

BIGGER, J.T., JR., ROLNITZKY, L.M., COROMILAS, J., WELD, F.M., AND DETURK, W.E.

It is the purpose of this chapter to examine two questions with respect to ventricular arrhythmias: (1) how should ventricular arrhythmias be classified? and (2) which ventricular arrhythmias should be treated? The first question has to do with deriving the useful information on the relationships between ventricular arrhythmias and outcome in observational studies or experimental studies. The purpose may be to estimate the association of ventricular arrhythmias and another factor, e.g., left ventricular dysfunction or cardiac death. Or, the purpose may be to judge the effect of a treatment on ventricular arrhythmias. The second question has to do with selection of patients for treatment in drug trials or clinical practice. We will consider both of the questions in the context of patients who are about to be discharged from hospital after myocardial infarction. We selected this group for several reasons. First, this is a common problem. Second, the year after myocardial infarction is a period of high risk for death. Third, ventricular arrhythmias are thought to contribute to post-infarction death.

METHODS

The methods of collecting clinical data and 24-hour ECG recordings have been detailed in previous publications (1). Also, the methods for analyzing ventricular arrhythmias by digital computer have been described previously (2). The present report will analyze 616 patients with acute myocardial infarction who were admitted to Columbia-Presbyterian Medical Center with myocardial infarction and followed for at least one year.

RESULTS

How should ventricular arrhythmias be classified?

Three major methods have been used to classify ventricular arrhythmias in past myocardial infarction patients: (1) The Lown grading system, (2) the HIP complexity classification and (3) an enumeration method.

The Lown Grading System. In 1971, Lown and Wolf proposed a grading system for ventricular arrhythmias encountered in ischemic heart disease (3); Lown and his colleagues have used the system up to the present time. The hypothesis underlying the Lown grades is: as the arrhythmia grade increases so does the risk for subsequent cardiac death. This grading system has been used for several small observational studies in ischemic heart disease. In 1975, Lown et al. proposed an extension of the grading system, an "arrhythmia equation." The arrhythmia equation enumerates the number of hours in each Lown grade and, in addition, provides some additional details about the arrhythmia in a 24-hour recording

(4). The arrhythmia equation has not been adapted for use in observational studies. Lown and Graboys, however, have suggested the arrhythmia equation as an ideal means of judging the results of experimental studies, for example with antiarrhythmic drugs (5).

The Lown system uses three VPD frequency partition values and four complex VPD features to grade arrhythmias (See Table 1). The three frequency categories (Ø, >Ø but <3Ø, >3Ø VPD per hour) and four complex VPD features give rise to 33 possible combinations (2^5+1). The Lown grading system aggregates the 33 possible combinations of frequency and complex features into seven grades in order of assumed prognostic significance. The system is mutually exclusive and hierarchical. Grades are assigned on the basis of the highest ranking characteristic. For example, if R on T is present, grade 5 is assigned regardless of VPD frequency or other complex features.

We tested some of the assumptions of the Lown grading system in patients with definite ischemic heart disease. One of the assumptions of the Lown grading system is that an increasing gradient of mortality from low to high risk should exist through the hierarchy of Lown grades. Table 2 shows that the death rate does not steadily increase as a function of Lown arrhythmia grade. The mortality rates are approximately equal in grades Ø through 3. The mortality rate is significantly higher in grades 4 and 5 than in the lower four grades ($p < Ø.Ø1$). Thus, the Lown grading system performs poorly in terms of defining a gradient of risk.

Table 3 displays the relationship between VPD frequency and one year cardiac mortality. The mortality rate increases as VPD frequency increases. Mortality rate steps up at 1 VPD per hour and again at 10 VPD per hour. A judgment about the best partition value depends to a great extent on the application at hand. If the low risk group is to be excluded from treatment and followed less often than other patients, 1 per hour is the better criterion: a very small proportion of the patients who will die or have new coronary events will be excluded from treatment or follow-up using this criterion. For antiarrhythmic drug trials, 10 per hour is a good criterion: about 25 per cent of the population is exposed to the risk of treatment and these patients already have a high VPD frequency and likelihood of dying. The Lown frequency criterion is set too high: only 14% of a post infarction population satisfy this criterion and only 29% of the deaths occur in patients with ventricular frequency $\geq$30 per hour.

Using Lown's grading system, frequency of VPD will hardly ever be used explicitly to estimate probability of death when these extrasystoles are numerous, because of the very strong association between high VPD frequency and complexity and from the mutually exclusive Lown grades. In our population, 86 of the 88 patients (98%) who had 30 or more VPD per hour (eligible for Lown grade 2) moved to higher Lown grades because they also had one or more complex VPD features.

One of the assumptions of the Lown grading system is

that frequency makes a trivial contribution to mortality risk when complex features are present. We tested this assumption using a frequency criterion of 1Ø per hour, a value that divides the population at the 75th percentile. We tested whether or not the presence of high frequency VPD increased the probability of dying in persons who were in Lown grades 4 and 5, i.e., those with the highest mortality rates. In Lown grades 4A, 4B, and 5, the persons who had 1Ø or more VPD per hour had a significantly higher mortality than persons in the same grade who had less than 1Ø VPD per hour. This result clearly indicates that VPD frequency continues to exert its adverse influence even in persons who have repetitive or R on T VPD.

Grades 3 to 5 of the Lown system represent aggregates of 3Ø distinct subgroups: grade 3, 2 subgroups; grade 4A, 4 subgroups; grade 4B, 8 subgroups; and grade 5, 16 subgroups. The 16 subgroups in grade 5 depend on the presence or absence of high frequency VPD, multiform VPD, paired VPD, and ventricular tachycardia. Feinstein has pointed out that, for prognostic stratification, subgroups should not be aggregated unless they are homogeneous with respect to outcome (6). Therefore, we examined the homogeneity of grade 5, because this group contained enough patients to make such comparisons useful. Three of the possible subgroups in grade 5 did not occur in our sample. The death rate among grade 5 subgroups ranged from Ø to 75%. Three <u>a priori</u> contrasts were made to test for homogeneity of mortality in Lown grade 5: (1) between those with high and those with low frequency

VPD, (2) between those patients who had repetitive VPD and those who did not and (3) between those patients with only R on T VPD and those with R on T VPD and all other complex VPD features /. Patients with high frequency VPD (≥30 VPD/hour) were 3.8 times as likely to die within a year of infarction as those with low frequency (p <Ø.Ø1). The 74 patients who had paired VPD had a 34% mortality rate compared with a 9% mortality in the 78 patients who did not (p <Ø.Ø1). The 34 patients who had ventricular tachycardia had a 47% mortality rate compared with a 14% mortality in the 118 patients who did not (p <Ø.Ø1). The 76 patients in grade 5 who had repetitive VPD or ventricular tachycardia, had a 34% one year mortality rate compared with an 8% one year mortality in the 76 patients who did not (p <Ø.Ø1). The 26 patients who had low VPD frequency and no complex feature except the R on T phenomenon had a 4% mortality, far below the overall 21% death rate in grade 5. There were 21 patients who had high frequency VPD and all complex features; the death rate in this group was 52%. The difference between these two subgroups also was highly significant (p <Ø.Ø1). In view of these findings, we concluded that there is very significant heterogeneity among the subgroups in Lown grade 5. Furthermore, high and low risk subgroups of grade 5 can be separated easily using results of 24-hour ECG recordings. The presence or absence of frequent and repetitive VPD are the most powerful determinants of mortality is Lown grade 5. Patients who have only R on T VPD are at extremely low risk.

Table 4

The HIP classification. The Health Insurance Plan of

New York (HIP) Study classified their ventricular arrhythmias into two groups: complex and simple VPD on the basis of a 1-hour Holter ECG recording (7). The complex category included bigeminy, multiform VPD, R on T VPD, and repetitive VPD. VPD recorded late in the year after myocardial infarction predicted mortality and that the relationship between complex ventricular arrhythmias and subsequent sudden cardiac death was still significant after adjusting for left ventricular dysfunction (7). Moss applied this classification to a group of patients who had survived a recent myocardial infarction and also found a significant relationship between complex ventricular arrhythmias in a 6-hour ECG recording and subsequent cardiac death (8). Neither author compared this classification to any other. We classified our 616 post infarction patients according to the HIP classification and also found a significant relationship with 1-year cardiac death (See Table 5). For 24-hour ECG recordings, the HIP classification is very sensitive but extremely non-specific. The mortality rate in the complex group is only one percentage point above the mortality rate for the population as a whole. The odds of dying in the complex subgroup is only 1.7 times as great as in the non-complex subgroup. Thus, this classification is too non-specific for selecting patients for intervention trials if 24-hour recordings are analyzed.

Enumeration method. Several groups including those at Washington University (9) and Columbia University (10) have preferred to fully enumerate the VPD counts and to charac-

terize separately the complex features as a function of time (in time intervals of 30 to 60 minutes). Over a 24-hour period, VPD frequency is usually summarized as an hourly rate by dividing the total number of each event by the number of analyzable hours in the record. Multiform VPD are summarized as the total number of configurations detected; R on T and repetitive VPD are usually noted as absent or present. When relating these ventricular ectopic events to outcome, the average VPD rate and absence or presence of various complex features are usually used.

Table 6 gives the probability of occurrence of each VPD feature in a nominal 24-hour tape and the conditional probability of one year cardiac mortality given the presence of each feature. Ventricular tachycardia poses the greatest risk. However, ventricular tachycardia is a rare event occurring in slightly more than 10% of the predischarge 24-hour ECG recordings after myocardial infarction. The likelihood of detecting ventricular tachycardia strongly depends on the duration of recording. The proportion of post-infarction patients having ventricular tachycardia is an almost linear function of the recording duration up to 72 hours of continuous recording. Thus, the HIP Study detected ventricular tachycardia in less than 0.1% of the 1,739 1-hour recordings made in the year after infarction (7). Anderson et al. recorded less than 10 episodes of ventricular tachycardia, i.e., <1%, in 915 6-hour ECG recordings taken about two weeks after myocardial infarction (11). Kleiger et al. found ventricular tachycardia in about 4% of

289 10-hour ECG recordings made between 10 and 30 days after myocardial infarction (9). Bigger et al. found ventricular tachycardia in about 11% of 430 24-hour ECG recordings made 10 to 25 days after myocardial infarction (12). It may be necessary to treat complex features as polychotomous variables to achieve optimum risk prediction when 48 or 72 hours of baseline recordings are analyzed. Using a 24-hour screening Holter, ventricular tachycardia is too rare an event to use as the screening criteria. Both frequent and repetitive (paired VPD or ventricular tachycardia) VPD have a 1-year mortality of 25% or more and are excellent candidates for intervention trials. The 19% and 21% mortality in the multiform and R on T groups is due in large part to repetitive VPD in these groups. When the patients with repetitive VPD are excluded, the mortality in these two groups falls to about 8%.

Which ventricular arrhythmias should be treated?

The decision to treat post-infarction arrhythmias should take into account the full spectrum of pathophysiology of coronary heart disease and the concept of competing risks. Patients who have had a recent infarction have a 10% chance of dying between hospital discharge and the first anniversary of the index myocardial infarction. The competing risks or hazards for death are ischemia, arrhythmia and left ventricular dysfunction. After myocardial infarction, a patient is likely to be at risk from all of these factors, although one or two usually predominate in a given patient.

The concept of competing risks has many implications for treatment strategies for patients in the year after myocardial infarction. We restrict ourselves here to a consideration of how this concept should be used in planning antiarrhythmic trials that have death as one of the major endpoints. Ideally, one should select for treatment the patients who will die arrhythmic deaths. To select patients for an antiarrhythmic drug trial who are at great risk for dying ischemic or ventricular failure deaths and at small risk for arrhythmic death is almost certain to confound the relationship between treatment and outcome. Even when we select the patients in whom arrhythmic risk predominates for an antiarrhythmic drug trial, some of the patients in both treatment and control groups will die of competing risks. If a high frequency of non-arrhythmic deaths occur in the treatment group it will require that the effect of treatment be quite large in order to become statistically significant.

The end point for the study will vary with the question being asked. If the question is: will reducing VPD frequency and complexity reduce the arrhythmic risk?, then sustained ventricular tachycardia or ventricular fibrillation or sudden cardiac death should be the end points. These end points will not distinguish between ventricular tachycardia or ventricular fibrillation that comes about because: (1) reentrant activation is initiated in around a large scar from (2) ventricular tachycardia of ventricular fibrillation that results from ischemia that is caused by coronary spasm, coronary thrombosis or from myocardial flow/demand inequi-

ties. Depending on the mechanism of action of the antiarrhythmic drug under study, differences in the mechanism of ventricular tachycardia and ventricular fibrillation could profoundly modify the result of the trial. If the question being asked is: what is the effect of antiarrhythmic treatment on overall mortality?, then total mortality or total cardiovascular mortality is the appropriate end point for the trial. Here more deaths will be required to show benefit for the antiarrhythmic treatment because deaths due to ischemic events and left ventricular failure are not likely to be prevented by treatment with conventional antiarrhythmic drugs. Using total cardiovascular mortality as the endpoint also permits the evaluation of lethal adverse effects of the treatment if the sample size is large enough to permit this analysis. Also, any ancillary drug effect on death due to ischemia or left ventricular dysfunction will augment the antiarrhythmic benefit. The vasodilatory or alpha adrenergic blocking properties of tricyclic antidepressants, quinidine, verapamil or amiodarone might add such a benefit. It follows from this discussion that a very careful categorization of the deaths is a strong requirement of post infarction antiarrhythmic drug trials.

From an analysis of the associations among various VPD characteristics and mortality (See Tables 3 and 6), we have shown that VPD frequency above 1Ø per hour or repetitive VPD have the strongest associations with mortality during the year following infarctions. To test the questions discussed above, either (1) frequent VPD $\geq$ 1Ø per hour) OR repetitive

VPD or (2) frequent AND repetitive VPD should be the target of an antiarrhythmic drug trial in the post-infarction years. Table 7 compares these two closely related criteria. There is not much to choose between them; the OR definition yields a larger sample size and greater sensitivity while the AND definition yields a smaller sample size and greater specificity.

SUMMARY

We believe that the baseline characterization of the patients who are enrolled into an antiarrhythmic trial should be as complete as is practical including measures of ischemia, left ventricular dysfunction and arrhythmia, each with some quantitative measure. This functional risk characterization can be used both for stratification of treatment groups and for covariate adjustment. In the case of arrhythmias a sensitive and specific tool should be used to detect and enumerate the arrhythmias. Complete and separate information should be kept on each arrhythmia characteristic in order to characterize the patients completely at baseline and for subgroup analysis if an overall difference is subsequently found between the treatment and control groups. We recommend that VPD frequency and repetitiveness be the characteristics qualifying patients for treatment; these two characteristics can either be OR'd or AND'd. The drug dose should be adjusted so as to ensure a specified degree of arrhythmia control. Depending on the question being asked either arrhythmic death or total cardiac death is the ap-

propriate end point for a trial. In either case, very careful follow-up and categorization of the deaths is needed in order to properly analyze and interpret the data from an antiarrhythmic drug trial.

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TABLE 1.
THE LOWN GRADING SYSTEM FOR VENTRICULAR ARRHYTHMIAS.

LOWN GRADE	FREQUENCY CRITERION	COMPLEX FEATURE CRITERION			
Ø	F=Ø	M=P=V=R=Ø			
1	Ø<F<3Ø	M=P=V=R=Ø			
2	F≥3Ø	M=P=V=R=Ø			
3	F>Ø	M>1	P=V=R=Ø		
4a	F>Ø	P>Ø	M≥Ø	V=R=Ø	
4b	F>Ø	V>Ø	M=P≥Ø	R=Ø	
5	F>Ø	R>Ø	M=P=V≥Ø		

TABLE 2.
RELATION BETWEEN LOWN GRADE AND ONE YEAR CARDIAC MORTALITY AFTER MYOCARDIAL INFARCTION

			ONE YEAR MORTALITY	
LOWN GRADE	N	PER CENT	N	PER CENT
Ø	1Ø2	17%	8	8%
1	127	21%	9	7%
2	2	<1%	Ø	Ø%
3	112	18%	1Ø	9%
4a	78	13%	14	18%
4b	43	7%	5	12%
5	152	25%	32	21%
TOTAL	616	1ØØ%	78	13%

TABLE 3.
RELATIONSHIP BETWEEN VPD FREQUENCY AND ONE YEAR MORTALITY AFTER MYOCARDIAL INFARCTION

FREQUENCY RANGE	NO. OF PATIENTS	PER CENT	DEATHS	
			NUMBER	PER CENT
Ø	1Ø2	15%	8	8%
Ø < Ø.1	59	9%	5	8%
Ø.1 - Ø.3	93	15%	5	5%
Ø.3 - 1.Ø	78	13%	4	5%
1 - 3	62	1Ø%	1Ø	16%
3 - 1Ø	74	12%	11	15%
1Ø - 3Ø	6Ø	1Ø%	12	2Ø%
3Ø - 1ØØ	42	7%	14	33%
≥ 1ØØ	616	1ØØ%	78	13%

TABLE 4.
HETEROGENCITY OF MORTALITY RATES IN LOWN GRADE 5.

COMPLEX CHARACTERISTIC	NUMBER OF PATIENTS		MORTALITY RATE		ODDS RATIO
	PRESENT	ABSENT	PRESENT	ABSENT	
VPD ≥ 3Ø/HR.	48	1Ø4	38%	14%	3.8
PAIRED VPD	74	78	34%	9%	4.9
VT	34	118	47%	14%	5.5
REPETITIVE VPD	76	76	34%	8%	5.7
ALL vs. NO OTHER COMPLEX FEATURE	21	26	52%	4%	18.6

TABLE 5.
RELATIONSHIP BETWEEN HIP ARRHYTHMIA CLASS OF ONE YEAR CARDIAC MORTALITY AFTER MYOCARDIAL INFARCTION

HIP CLASS	DEAD	ALIVE	TOTAL
COMPLEX	70	448	518
NOT COMPLEX	8	90	97
TOTAL	78	538	616

MORTALITY/COMPLEX = 14%
MORTALITY/NOT-COMPLEX = 8%

ODDS RATIO 1.67 ($p < 0.05$)

TABLE 6.
RELATION BETWEEN VPD CHARACTERISTICS AND ONE YEAR CARDIAC DEATH.

	PATIENTS		DEATHS	
CHARACTERISTIC	NO.	PER CENT	NO.	PER CENT
VPD $\geq$ 10/HR	148	24%	35	24%
MULTIFORM	279	45%	52	19%
PAIRS	187	30%	42	22%
VT	72	12%	20	28%
R on T	152	25%	32	21%

TABLE 7.
CRITERIA FOR TREATMENT OF VPD AFTER ACUTE MYOCARDIAL INFARCTION

VPD	PATIENTS		DEATHS		ODDS
CRITERION	NO.	PER CENT	NO.	PER CENT	RATIO
F10	148	24%	35	24%	3.1
REPETITIVE	201	33%	45	22%	3.3
F10 or REPETITIVE	236	38%	50	21%	3.4
F10 and REPETITIVE	113	18%	30	27%	3.4

STUDY DESIGN FOR PATIENTS WITH CHRONIC VENTRICULAR ECTOPY: DETERMINATION OF EFFICACY AND TOLERANCE

Joel Morganroth, M.D.

Over 400,000 sudden cardiac deaths occur in the United States each year in which the majority are premature and without warning. Sudden electrical death is the leading cause of death in the 20-64 age group. Since the majority of these deaths do not occur as the consequence of end-stage cardiac disease, the prevention of the ventricular tachyarrhythmia which is responsible for the majority of these events should have a major impact on the prevalence and significance of this disease.

It has been clearly shown that the patient at highest risk of sudden cardiac death is the individual who has both underlying electrical and mechanical (or structural) cardiac dysfunction.[1]

In this particular manuscript we will address the clinical problem of ventricular premature complexes as a sign of electrical instability. These may occur in patients with sustained ventricular tachycardia which cause immediate symptoms and can thus be called "hemodynamically significant ventricular ectopy". In other patients ventricular ectopy may be chronic without causing immediate hemodynamic consequences even if associated with non-sustained ventricular tachycardia but can place an individual at high risk of sudden death. These individuals clearly warrant antiarrhythmic suppressive therapy if it can be demonstrated that amelioration of the electrical instability prevents sudden cardiac death. Once antiarrhythmic agents are available which are effective, safe and well-tolerated for long periods of time, we will have the ability to test this hypothesis.

Patients with hemodynamically significant ventricular tachyarrhythmias cannot usually be studied with placebo periods for baseline control and often require invasive electrophysiological

testing for rapid determination of therapeutic effect. Patients with chronic ventricular arrhythmias can be studied as outpatients and subjected to placebo periods. Non-invasive methodology using primarily ambulatory (Holter) monitoring and occasionally exercise testing are logical tools to define efficacy in this group. This manuscript will address only the evaluation of patients with chronic non-hemodynamically significant ventricular ectopy.

AMBULATORY MONITORING AS A METHOD TO DETERMINE EFFICACY OF NEW ANTIARRHYTHMIC AGENTS IN PATIENTS WITH CHRONIC VENTRICULAR ARRHYTHMIAS

Ambulatory monitoring has been shown to be the most effective means of defining the presence of ventricular premature complexes and quantifying their frequency.[3] The definition of antiarrhythmia drug efficacy is based on the extent of quantitatively determined reductions in the prevalence of ventricular ectopy on therapy as compared to the control period.[4] Ambulatory monitoring requires careful quality control in the generation of quantitative data.

The quality of the Holter monitor recorder and recording tape must be reviewed to ensure proper accuracy of the analysis of the ambulatory monitoring tapes. Soft-ware systems have been utilized in recent years as the most precise way of determining accurate counts of ectopic ventricular frequency. With rapid changes in technology and limited ability of individual laboratories with small volumes of analyses to provide the most accurate analysis, central research service laboratories have become the primary means of obtaining this research data. The use of central laboratories for all data analysis has now become a standard policy in cooperative clinical trials to ensure lack of bias and the highest quality of diagnostic data. Central research Holter monitoring services should frequently determine the accuracy and repeatability of their data analysis by reintroducing into their reading schedule 24-hour ambulatory tapes which have been read in real time and serve as gold standard references for their analysis system. Repeat evaluation of the same tapes should also be used to test standardization and repeatability. This type quality control

program should be used in any research ambulatory monitoring laboratory and a subset of the tapes can always be subjected to analysis by other laboratories.

Using ambulatory monitoring as the model to determine antiarrhythmic efficacy in patients with chronic ventricular ectopy requires precise definitions. Utilizing quantitative ambulatory data and applying biostatistical techniques has allowed for a more logical and repeatable approach to the definition of antiarrhythmic efficacy.

Individual patient data comparing the effect of an antiarrhythmic drug to a control period is the basis for the reporting of drug efficacy when comparing active agent to placebo Efficacy is defined at a certain level of reduction in ectopy frequency.[4] The number of individuals treated with an agent who respond will define the percentage of patients who achieve drug efficacy.[5]

The patient population in chronic arrhythmia studies is usually so heterogeneous that it is not advisable to group drug and placebo comparison data to obtain mean differences since this technique often masks the observations of indivdiual patient variability and adverse reactions which cause an increase in ectopic frequency. Thus,the preferred approach to the analysis of efficacy of new antiarrhythmic drugs is to determine the percentage of individual patients on active drug that have reache a certain level of therapeutic efficacy.[5] Most of the currently released antiarrhythmic agents in the U.S.A. for suppressing chronic ventricular arrhythmias appear to significantly decrease such arrhythmias in approximately 50-75% of treated patients. About 5-20% of such patients will have the adverse reaction of an increase in ventricular ectopic frequency.[6]

Multiple Holter monitoring on placebo has shown that most patients have a high frequency of spontaneous variability in ventricular ectopic frequency and thus guidelines are required to determine the level of reduction required to show drug effect. (Table 1) Using complex statistical methodology and multiple

data sets obtained during placebo periods in a cross-sample of general cardiac patients a certain percentage of reduction in ectopic frequency is required to avoid changes solely due to spontaneous variability. The percent decrease required for efficacy will depend upon the type of arrhythmia (i.e., simple vs. complex), length of recording obtained on placebo and active agent, and whether pooled patient data or individual data are utilized. Individual patient data determined by frequent Holter monitoring on placebo will demonstrate the degree of spontaneous variability in arrhythmia frequency in the individual subject.[7] At least two 24-hour Holter monitoring sessions are required (with our preference being 72 hours) on placebo. It has also been shown that patients with frequent ventricular ectopy (usually greater than 1000 per hr. per day) have much less spontaneous ectopic variability and thus a much less degree of ectopy reduction is necessary to define drug efficacy.[4] Patients with lower frequency of ventricular ectopy have a higher rate of spontaneous variability.

TABLE 1

REDUCTION IN VENTRICULAR ECTOPY
REQUIRED TO SHOW DRUG EFFECT

Length of the Ambulator Monitoring Recording		% Reduction Required For		
On Placebo	On Drug	VPC	VC	VT
12	12	-89	-82	-71
24	24	-83	-75	-65
72	72	-65	55	-45

VPC=Ventricular premature complexes
VC=Ventricular couplets
VT=Ventricular tachycardia

We recommend that a 75% decrease in ventricular ectopic frequency be used as the frequency rate in patients with chronic ventricular ectopy to define drug efficacy.

PATIENT INCLUSION CRITERIA FOR STUDY DESIGN

Taking into consideration the frequency of ventricular ectopy and its degree of spontaneous variability, we recommend that patients be entered into chronic antiarrhythmic protocols wh have at least 30 premature ventricular beats (VPBs) per hour per day. While Bigger et al[8] have shown that patients after myocardial infarction with 10 or more VPBs per hour per 24 hours mark individuals at an increased risk of sudden cardiac death, the higher frequency of spontaneous variability using this criteria in this population will require a higher degree of VPB reduction to accurately determine drug effect.

Patients with chronic ventricular ectopy with increased ris of sudden cardiac death are the primary focus in trials of experimental antiarrhythmic drugs. However, since the prevention of sudden cardiac death by antiarrhythmic drugs has not been clearly demonstrated in such patients, it is perfectly acceptable to allow such patients to undergo placebo control period (to define prevalence and type of VPBs during baseline). This placebo period should be conducted at least seven days after stopping prior antiarrhythmic agents.

In light of the frequent use of beta blockers for angina, hypertension and their frequent use in patients post-myocardial infarction, we believe that beta blockers can be used concomitantly with new antiarrhythmic agents (unless a known drug interaction exists) as long as their dosage is not changed during the study. This would also hold true for Digoxin and Coumadin though the latter two drugs require frequent measurement of the blood level to detect important drug interactions.

DESIGN OF TRIALS TO DEFINE EFFICACY IN PATIENTS WITH CHRONIC VENTRICULAR ECTOPY

Placebo controlled randomized double-blind clinical trials

are obviously preferred in all studies testing antiarrhythmic agents in patients with chronic ventricular arrhythmias. Several designs are possible.[9] The simple parallel trial involves the random allocation of patients into either treatment or control groups. This design yields little information on individual patient response and the power is poor. The extended parallel design allocates patients to control or treatment groups after their response to placebo has been defined and this type of study gives information on group and individual patient response. (Figurel) Its power depends on the magnitude of the variance of individual differences at baseline and in general the heterogeneity of patients with chronic ventricular ectopy usually represents a drawback to this model unless large numbers of patients are studied; thus, increasing recruitment problems. In a simple crossover design each patient is given both the active agent and placebo in random order, thus decreasing drop out rate and easing recruitment problems. This design is more powerful, requires less numbers of patients and thus costs less to perform. Unfortunately, patients may still have persistent effect from the prior intervention which can be overcome by extended cross-over design in which adequate placebo washout periods are introduced between the two arms of the protocol. (Figure 2) When this model is used with antiarrhythmic agents, the return of ventricular ectopy by Holter monitoring can identify lack of prior treatment effect. This is the preferred study design in our opinion.

Initially, short-term studies should be conducted to define active drug efficacy against placebo. Early studies can be accomplished in a Clinical Research Unit setting in which the new antiarrhythmic agent is given to patients with chronic ventricular ectopy using a placebo/active agent/placebo simple blind design. When efficacy and short-term safety are demonstrated, then the new agent should be used in out-patients in which placebo control/double blind trials are followed. After a placebo control period, dose titration can be accomplished by giving active agent using one 24-hour monitor session each week using at

least 48 to 72 hours of ECG monitoring during the intial placebo week. One can then utilize the most effective and safe dose found in patients over long periods of time with Holter monitoring obtained at least every one to three months. Placebo reintroduction at six months is quite appropriate. Other more complex study designs can be conducted after the initial placebo/active agent/placebo period. An alternating Latin Square Design can be used in responders of the initial phase in which random ordered dosing intervals of active agent and placebo are given. Other designs that have been used consist of periods of placebo/active agent/placebo as one arm compared to placebo/placebo/active agent as the other. This is a cross-over placebo active agent trial. These more complex designs have some usefulness in ensuring a dose response but their major shortcoming is the higher cost for studies required.

Comparative antiarrhythmic efficacy trials against the standard agents quinidine or procainamide can use simple models. Either extended parallel or cross-over designs are possible. Short-term studies over a few weeks (e.g., 3-5 weeks) are sufficient to define drug efficacy and need not be conducted over longer periods of time. Extended cross-over designs are preferred. Drug titration in these comparative studies can be accomplished with alternate week dosing (e.g., Week 1, dose 1, Week 2, dose 2, depending on Holter monitor results at Week 1); however, a fixed dose is more simple and less fraught with study error.

Long-term efficacy and tolerance over months in open label trials can be conducted using ambulatory Holter monitoring to detect changes in drug efficacy at periods such as one, three, six, nine, and twelve months. One can also utilize an event recorder such as a transtelephonic ECG device which allows patients to provide ECG data during symptoms or between full monitoring sessions.In addition to long-term evaluation of signs and symptoms full drug tolerance and safety requires consideration of the use of the new antiarrythmic agent in patients with known marked left ventricular dysfunction. Careful non-

invasive measurements[10] (e.g., echocardiography and/or radionuclide angiography) both prior to and after drug dosing may determine the negative inontropic potential of the anti-arrhythmic drug. Drug interaction studies with Digoxin, beta blockers and anticoagulants are essential. Tolerance must include the evaluation of routine laboratory blood and urine tests and possibly levels of antinuclear antibodies. Evaluation of the ambulatory Holter montior data searching for increased frequency of ventricular arrhythmias as an adverse reaction of patients on new antiarrhythmic agents must be done.

Thus, simple study designs can be formulated to rapidly evaluate the efficacy and safety of short and long term use of new antiarrhythmic agents in patients with chronic ventricular arrhythmias. Once an effective and safe agent is available, the test of whether treatment of the electrical instability in patients with chronic ventricular arrhythmias prevents sudden cardiac death will be possible.

FIGURE ONE

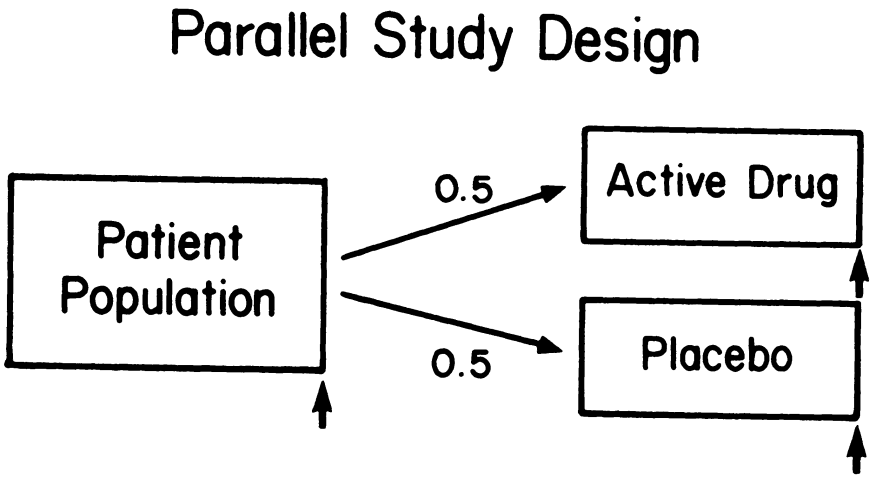
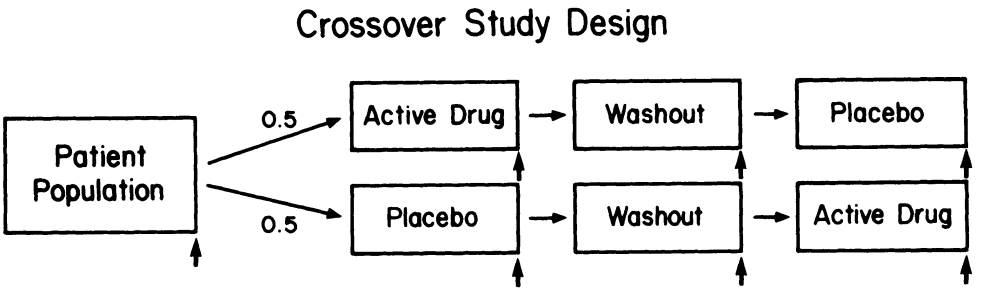


FIGURE TWO



BLACK ARROW REPRESENTS TIMES OF EFFICACY MEASURES

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1. CHRONIC TOLERANCE TO ANTIARRHYTHMIC THERAPY
2. HOW TO HANDLE EMERGENCY DRUG REQUESTS

STEWART J. EHRREICH, PH.D.

I. INTRODUCTION: CHRONIC TOLERANCE

The topics for presentation today are rather diverse but first we will discuss the problem of tolerance.

A. Definition

Tolerance to therapy of any type usually refers to the development of a gradual loss of control (therapeutic failure) by the drug over a certain time period.

B. General Concepts

In the pharmacologic sense, tolerance usually means that although drug concentration at the site of action (presumably the "receptor" responsible for the series of events leading to a particular physiologic occurrence) is fairly constant, there is a failure to maintain constant drug action. Clinically there is a loss or partial loss of drug effect and exacerbation of the patient's condition.

In the case of antihypertensive agents, tolerance to drug effects manifests itself by an elevation of blood pressure, sometimes in a dramatic way or "overshoot" above the predrug level, but more often by a gradual failure to control pressure until drug effect is almost totally lost. Such effects are documented in the literature but loss of control during treatment for ventricular arrhythmias is not clearly documented and represents a new area for research.

Often the tolerance to one drug leads to a "cross-tolerance" to drugs of similar type, or even different types which act on the same pharmacologic receptor. Thus, it is often difficult to determine if there is pharmacologic tolerance since the introduction of a different drug may still show the tolerance phenomenon.

Failure of the physiologic mechanism to be able to respond to any intervention may lead to a type of pseudotolerance in which it appears that the drug has begun to fail, when the actual case is that no intervention will be effective. Examples of this are the failure of peripheral vasodilators to be effective because of the volume expansion which reflexly occurs.

In the case of antiarrhythmic agents it is particularly difficult to assess tolerance because of the following complicating factors:

1. The drug effect may not be lost but the agent may actually be inducing the arrythmia because of direct arrhythmogenic effects of many (all??) antiarrhythmic agents.

2. There may be a worsening of the disease state which led to the arrhythmia in the first place.

3. Induction of a drug removal pathway (usually by some metabolic event) may have occurred which will reduce the effective drug concentration at the receptor site. This occurs also as a result of the onset or exacerbation of another disease state which may alter plasma half-life.

4. Another medication, "B", introduced during therapy with drug "A" may now be antagonizing the effect of A by any number of direct or

indirect mechanisms. This may also occur if the concurrent (antagonistic) medication, B, becomes more effective for various reasons. An example of this is the antagonistic effect of a non-steroidal antiinflammatory drug, such as indomethacin, which blocks the prostaglandin mediated effects of furosemide.

5. The patient may have stopped medication or reduced the dosage or changed his dosage schedule, unbeknownst to the physician.

6. There may be a manufacturing or stability problem with the medication or another manufacturer's drug may have been substituted which may have a different pattern of bioavailability. This may be particularly troublesome with the advent of certain generic substitutes or the use of drugs made by unapproved clandestine manufacturers.

The problem of tolerance to chronic (usually oral) therapy of an antiarrhythmic agent is rarely then in the recognition of the problem, since it is clear that the arrhythmia has either worsened in intensity or frequency or that it has degenerated to a more ominous or life-threatening situation. The problem is which of the causes, enumerated above, is/are the reason(s) for the failure of therapy to be effective.

The following are methods recommended to determine what might be the cause of tolerance.

Table I[1]

Problems in Evaluation of Antiarrhythmic Profiles of Activity

1. Most agents have relatively narrow therapeutic safety margin.
2. Effects of successful therapy difficult to assess and document.
3. Therapeutic range (e.g. plasma levels) not known for some, difficult to measure for others.
4. Variability in biopharmaceutic parameters.
5. How to recognize "therapeutic failure".

C. Therapeutic Plasma Levels

Therapeutic plasma levels have been published for a variety of antiarrhythmic agents. These levels are different for different methods of assay and also vary with the investigator and from patient to patient. Ball-park figures however are available for the following agents:

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[1] Brown, J.E. and Shand, D.G., Therapeutic Drug Monitoring of Antiarrhythmic Agents, Clin Pharmacokinetics 7:125-148, 1982.

Quinidine	-	1 to 5 ug/ml
Procainamide	-	4 to 10 ug/ml
Disopyramide	-	3.7 ug/ml (margin of toxicity)
Lidocaine	-	1.5 to 5.0 ug/ml
Mexiletine	-	0.5 to 2.0 ug/ml
Phenytoin	-	4 to 24 ug/ml
Propranolol	-	10 to 1,000 ug/ml

The wide variability in therapeutic levels, especially in the case of propranolol indicates that responders to therapy may be found at both ends of the therapeutic spectrum. Similarly there is a fine line between therapy and toxicity. Often there is no line at all.

D. Assessment of Therapeutic Failures Not Due to Inadequate Plasma Levels

This problem confronts not only the sponsor of an investigation but also the regulatory agency requiring the demonstration of success/failure with a new drug. At the present time the use of programmed electrical stimulation (PES) to elicit predictable, potentially treatable arrhythmias seems a reasonable approach to this problem. Patients becoming refractory to continuous treatment of a formerly effective compound might have to be subjected, at the point of obvious escape from control, to PES to determine if other compounds or combinations of compounds will be effective despite tolerance to the original medication. While this does not provide a simple mechanism to determine the reason for therapeutic failure its use would provide a means to successfully treat the patient. It is hoped that the other participants in this symposium would consider this procedure and comment on its

use/potential usefulness for determination of tolerance during the course of therapy in patients who become refractory.

II. INTRODUCTION: HOW SHOULD ONE MANAGE EMERGENCY DRUG REQUESTS AND THEIR DATA?

The Food and Drug Administration is aware that there may be good reason to use an investigational drug in patient care, i.e., not in a formal investigation, before complete data on effectiveness and safety are available. The usual reason for an emergency drug request is the combination of a patient with a life-threatening disease who has exhausted all standard therapy, and the availability of a promising new agent with some evidence of usefulness in the condition. A request for use of a drug in such cases is usually called a request for "emergency" or "compassionate" use. Patients with life-threatening cardiac arrhythmias provide a particularly common source of these requests, and the gravity of the situation often requires quick action. The problem is thus not only to obtain permission to treat the patient with the experimental compound, but to find out how the drug can be obtained in as short a time as possible.

Emergency uses of drugs are a source of some discomfort to both FDA and the pharmaceutical industry: to FDA because these uses cannot be closely monitored and because information about the drug is incomplete; to industry because very sick patients may die or have adverse events and raise troubling questions about the drug. Nonetheless, FDA and the pharmaceutical industry have almost always concluded that a seriously ill patient cannot be denied that medication which may offer a reasonable possibility of benefit. It is essential however, that physicians using

drugs under these circumstances carry out their obligations to their patients, to the drug manufacturer, and to FDA by monitoring patients closely and supplying needed information.

The recent requests to FDA for use of amiodarone in patients refractory to other therapy has reached over 300 in number. The mere logistics required to handle these IND's is sizeable. The establishment of an office of Orphan Drug Development, headed by Dr. Marion Finkel represents a concerted effort on the part of the Agency to handle the serious problems posed by the failure of certain drugs to be sponsored by a manufacturer.

There are established procedures in our Division and in the rest of the National Center for Drugs and Biologics, for considering emergency request promptly. If an emergency occurs during non-business hours there are ways to contact the appropriate individuals, but this is far more difficult and every effort should be made to reach us between 8:00 a.m. and 4:30 p.m.

Emergency use of a drug can be carried out either under an emergency protocol developed by the drug manufacturer, if such a protocol exists, under an application by the treating physician. Most antiarrhythmic drugs, because of their nature, do have existing emergency protocols including entry criteria, monitoring requirements, etc. Whenever possible patients will be treated under such protocols, rather than under a separate individual investigator application, as it is far easier for us and it keeps all the data together. In addition, the investigator usually need contact only the manufacturer to use the drug under these protocols.

A. Mechanisms for Obtaining Investigational (non-approved) Antiarrhythmic Agents

1. Does an Emergency Protocol Exist? Once a physician concludes his patient needs an investigational agent, he should contact either the drug manufacturer or consumer safety officer (CSO) within the Division of Cardio-Renal Drug Products. If an emergency protocol exists, FDA will ask the investigator to call the pharmaceutical company, whereupon the company can make arrangements for the drug to be shipped at once if the patient meets the emergency protocol entrance criteria. Sometimes a lengthier written submission will be requested. The investigator must agree to: follow the company's protocol as closely as possible and to report fully all details of the case and all resulting data should be sent to the company. They will handle the necessary paper work for FDA purposes from that point on.

In the event that no emergency protocol exists the manufacturer may be willing to request a single emergency use under its own IND or may ask the physician to file one himself. In that case, FDA will need to review the proposal.

2. Mechanism to Obtain a "Compassionate IND". In the absence of an existing emergency protocol, the FDA medical officer, supervisory medical officer, or Division Director may determine that the proposed use should be permitted. The drug manufacturer will then be told he may provide the drug and describe the case in writing to use the drug, or, if the physician obtains his own IND, an IND number will be obtained to identify the drug investigator and purpose of the study, which is called a "compassionate IND". Once the number is given, the drug will be shipped

to the investigator by the company. Such an IND may list specific patients or specific characteristics of the patients who will be transferred. Only those patients indicated in the IND are to be treated and unused drug is to be returned to the company. The investigator is not authorized to administer the agent to other kinds of patients or to transfer the drug to another investigator. The investigator is held accountable for the entire supply of the drug which he received.

3. Supplying Information on the Completed Investigation or "Compassionate Use". If patients have been treated in an emergency situation the investigator will not have been able to provide the usual required information ahead of time so that, as soon as possible, he should provide the completed FDA form 1571 (for his own IND) or 1572 or 1573 if he joins the manufacturer's IND; these forms will include the study protocol used and, if available, results obtained. If more time is available, forms 1571, 1572, and/or 1573 are filed ahead of time.

B. Analysis of Data Obtained From Emergency Protocols

Much of the data derived from emergency protocols comes from studies with few patients per investigator and has provided little useful information on effectiveness, some on safety. Emergency protocols typically lack the sophistication of approach and analysis needed to be useful. Perhaps this need not always be the case. Efforts should be made, where possible to coordinate clinical exposure of frequently used drugs so that the data generated will be ultimately useful in an eventual New Drug Application. The Agency realizes the difficulties in such a cooperative effort and is considering all kinds of mechanisms to solve the problem. Meanwhile, however, very little data generated in the

emergency protocols is useful for the analysis of drug safety and efficacy and this is a very unfortunate situation. Those assembled here today might consider mechanisms to help solve this problem.

Dr. Harrison: I want to complicate the efficacy question just a little more. In symptomatic patients, one can use symptoms, to judge efficacy. Another efficacy definition is to reduce all ectopic beats and with some of the new agents, that seems possible, but probably not a practical approach to demonstrating efficacy. In another approach Dr. Morganroth mentioned, we can decrease the number of VPCs by 75% and complex forms by 100%. A fourth means is to get therapeutic blood levels within the therapeutic window as described by Dr. Woosley. I want to present another biostatistical approach that we have used and I think it will complicate this discussion even more, but I think it may shed light on this problem. That is using a linear regression analysis with determination of the 95 or 99% confidence intervals of variability for measurements made on placebo and a baseline period. This approach was devised by Dr. Helen Kramer of our institution. Using a plot of the baseline average PVC frequency per hour on a placebo. One can see in patients up to 1000 PVC's per hour to something on the range of 10 PVC's per hour and using this analysis of the observations made while in a baseline period versus the placebo period one can establish these confidence intervals. If you are looking at the sensitivity of this kind of method you really have to look at the point where the 99 or 95% confidence interval crosses the baseline and you see this corresponds pretty much to what Dr. Bigger said when he was talking about 10 PVC's per hour being a threshold level for increased sudden death. I think this approach can be helpful in looking at efficacy in a comparative way, then in looking at efficacy in a single drug, although I think it will apply there too. This kind of biostatistical transformation and this kind of biostatistical handling of the data will also be one way to approach the problem of spontaneous variability. I think it is an alternate approach which should be given a test.

Dr. Woosley: I think this is a nice approach and I think it has a great deal of application in doing group comparisons. I am not a biostatistician, so I am not sure I am on sound grounds, but I have great reluctance in looking at individual patients with this kind of analysis, because your regression lines establish the variability for a population so I think you can make a comparison to another population. It you try to go into the data with a given patient, you haven't established the variability for that patient and to say that you don't have a drug effect or you do have a drug effect for a given

patient, because they are not within or without those limits, I think is statistically unsound.

Dr. Morganroth: One other problem is that if one is trying to use a level of 5 to 15 PVC's per hour in patients, the analysis of such data by Holter monitoring has its greatest error rate in that range.

Dr. Harrison: The threshold value of 10 per hour is not the area in which this approach would this would be maximally effective. Obviously if we used the criterion which you have used of 30 VPC/hr that would be better. Unless you define your population very carefully and it is very homogeneous, you could not use this approach for individual patients. For comparative studies and group comparisons, I think it is an ideal technique for that.

Dr. Kostis: To confuse the issue a little more, I would like to ask about the optimum duration of monitoring, especially when one intends to identify patients at risk of mortality. Dr. Bigger told us that using complexity alone has a very low specificity and that 75-80% may have complexity if monitored 24 hours. On the other hand, Ruberman's data showed that only 25% of high risk patients had complexity when monitored for 1 hour.

Dr. Bigger: That is a difficult question and still not entirely settled, but for example, for frequency, probably anything 6 hours or greater is enough to characterize a population at baseline for observational studies and probably insufficient for a baseline for interventional studies, where you are going to look at drug effects. The frequency is not so difficult however when compared to rapidity forms, for example ventricular tachycardia. The detection rate for ventricular tachycardia rises and then begins to tail off in the third day. Our own data show it is just continuously rising in a straight line for 3 days, so detection of rare events like ventricular tachycardia requires a very long time of monitoring. It rises almost linearly as a function of time out through 72 hours. Such data fits a Poisson distribution and you could use the derived time constants to show precisely how long you would have to record to detect an event if it was occurring at any given frequency and those models are sort of useful for making estimates.

Dr. Morganroth: What would you suggest if you were designing a protocol for the number of baseline Holter monitors?

Dr. Bigger: I think that there is a long list of factors that enter into that discussion and I guess you have enumerated them so I won't. I would just mention that. I think either 24 or 48 hours is a good compromise.

Dr. Morganroth: Dr. Lipicky, what would you use if you were designing such a trial?

Dr. Lipicky: Well, it is difficult to really answer that. Obviously, I thin the real question is what is the focus of the study? If the purpose of the study is to detect some influence on mortality and one is interested in identifying those patients who have the highest risk of dying and only includ them, you would use an entirely different means of monitoring and judging efficacy than if the purpose of the study was simply to detect an alteration in VPB rate. I think that there is room for multiple criteria of efficacy and that there really is not a singular criterion that one needs to adopt for there are clearly different purposes to studies.

Dr. Winkle: It is my personal opinion that the degree to which spontaneous variability affects these drug studies has been grossly overemphasized. I think it really is important only in drugs with marginal effectiveness. The reality of most of the drugs that I have dealt with in the last few years is that they suppress, ventricular ectopic beats and short salvos in a very high percentage of patients to whom they are given. It doesn't take 6 biostatisti cians to look at 20 patients and you give the drug and 18 had PVC's totally suppressed to tell you that the drug is working. In fact, with appropriate placebo controls, I would be happy with an hour of ECG data with frequent PVC's, you give a drug, they virtually all go away, and on the placebo day, only 1 or 2 out of 20 patients have such a decline, I just think we have made far too much out of it and we are making the studies much more expensive ther they need to be. It is very important if your initial screening study suggests that the drug isn't terribly effective for suppressing PVC's, then you have to go into all the complex statistics, but for most of the drugs we are seeing now, I just think too much is being made of it.

Dr. Harrison: Roger, would you comment on what Tom Bigger said about the number of days of monitoring is needed in a control period?

Dr. Winkle: I think for most studies, I would agree with his numbers of 1 or 2 24-hour Holters. I do think there is the diurnal variation and other thing to look at. I would make one comment in that our data in the post-MI patient shows that most of the complex forms did seem to reach some plateau by 3 days but ventricular tachycardia actually was still rising and in the third day, w picked up a very large new group who hadn't had it in the first two days.

Dr. Lipicky: Along those lines, one question would be whether that kind of criterion, say 24 to 48 hours of monitoring is based on the idea that if one

looks at this 24 to 48 hour interval that one can reasonably expect to find the same incidence or the same kinds of arrhythmias three months hence, or is it based on the probabilities of identifying something that one didn't see in the first 5 minutes. Can you respond to that?

Dr. Morganroth: We have actually looked at that, in that we took a series of patients and monitored them on placebo three months apart and the statistical evaluation of their arrhythmia frequencies demonstrated that one could almost consider them totally different patients. That is, an individual patient's arrhythmia profile at month 1 was entirely different at month 3 so that one could statistically consider them as totally different patients. That was one of the reasons that I suggested a placebo re-introduction as part of long term trials, because one can be very surprised as to the outcome. As we sometimes see in short term studies, when you look at the final placebo period, PVC's may not always come back at all. I think that spontaneous variability is high enough that this becomes an important issue.

Dr. Lipicky: If that is true, the duration of time that one needs to measure at baseline is relatively unimportant, isn't it?

Dr. Morganroth: I am personally convinced that 48 hours of monitoring is necessary at least in part for logistic reasons. Not only does one insure a diurnal variation, but with two Holters, you are more likely to get useful data since about 10% of the tapes may fail. Also you might look at a patient very differently if on one day he has 10 and the next day 1000 VPCs/hr versus the a similar patient with 60 then 60 VPCs/hr. I personally find a lot of information in two monitors and I think that amount is practical to obtain.

Dr. Atkins: Joel, when you were talking about the carry-over, you sort of intimated there is relatively little placebo effect in arrhythmias in comparison to angina and other hypertensives. I would like to disagree a little bit. I think because of the psychological elements, it's role in inducing arrhythmias, I think you see both a positive placebo effect and a negative placebo effect, particularly in long-term cross-over studies. You will see in long-term cross-over studies some patients who, although they are asymptomatic take their pulse, notice they are having PVC's and get progressively depressed as they continue in the study and actually see their arrhythmias increasing because of this depression.

Dr. Morganroth: During a washout period in a cross over study using an objective end point as Holter monitoring with the study's purpose to see if a drug suppresses PVC's if the washout period shows a high prevalence of PVC's

as it did during the initial placebo period, is unlikely. We see little change from baseline to placebo data.

Dr. Reid: I would like to go back to a point that has to with the variance that one experiences in trying to set up one of these studies. We have had a number of placebo cures, which I think most other people have as well. Likewise, we see some patients if you do a series of monitors over several days or weeks, a small coefficient of variation of the PVC's whereas in other patients, it has wide fluctuations. To me this underscores the problem of the population definition which we typically do not take into account in some of the early phase studies. In other words, what is the substrate abnormality that pre-exists and how carefully has one looked into this population prior to entering these patients in study. It can be done at relatively cost-effective methods which might in fact tend to reduce the total cost of the study. To me it seems we spend too little attention to defining the substrate which pre-exists. We just go out and count PVC's, we give a few pills, make out some more PVC's, we get upset if there is nothing returning in placebo.

Dr. Morganroth: I agree with that entirely. More attention should be devoted to looking at the baseline using non-invasive echocardiographic or radionuclide studies to characterize ventricular function.

Dr. Temple: Joel, you indicated that you thought that people with asymptomatic arrhythmias probably weren't good candidates for electrophysiologic testing and I guess it seems to me that that conclusion is one that ought to be tested since for no other reason than that many of the treatments can make arrhythmias worse or provoke inducibility where there was none. I wondered if Dr. Bigger could help a little on that question by telling us whether the well-characterized patient populations you described have been studied with respect to their inducibility. In other words, would invasive testing help you choose therapy for some of the high risk groups you talked about. Are they in fact inducible in any great proportions.

Dr. Bigger: There are a number of people in the audience who could comment, but somewhere along the way Dr. Harrison and I just want to register our disagreement about a large placebo effect on arrhythmias and at least certain well-characterized populations, that is the kind of patients that are subject to, who reproducibly have ventricular arrhythmias of a non-hemodynamically important type that are used over and over in drug trials and in chronic studies after myocardial infarction over the next couple of years. The arrhythmic variation over a year's time is much much less than you would think

given the changes in the baseline condition, the drug's treated, the emotional states, the changes in life that are going one, they are remarkably stable in about 65% of the patients. There are many striking examples. Don and I were just talking, at least within one week two recordings, one not on placebo and one on placebo, we find no more variation there then we do if we just take two recordings in a week with no placebo treatment, sitting around during that time. We don't find any difference at all due to placebo in a short interval of time, it increases when you look at placebo period like 6 months or 12 months later, but it still is remarkably stable in about 65% of the patients even at a year's interval. In regard to Dr. Temple's question, the few people that have attempted to induce patients say before the time of discharge, after acute myocardial infarction, there are several such studies ongoing and have been casually reported in discussions, etc. seem to be 20% of the time of hospital discharge that are inducible, that is with programmed ventricular stimulation, will have either ventricular tachycardia sustained for say more than 6 repetive beats or will have ventricular fibrillation and I think this is an area where first the findings have to be confirmed, the estimates of those proportions have to be made with better confidence limits and then one has to think about how this compares to non-invasive testing. Whether it is good or not, that data is not yet available and then one can proceed to think about how to include this type of evaluation in the overall intervention trials of some form or another.

Dr. Morganroth: Bob,your suggestion that a different model, such as electrophysiologic testing might be more predictive of drug efficacy relative to sudden death is of course very interesting but unproven. The potential of taking patients with chronic asymptomatic arrhythmia who have non-sustained ventricular tachycardia and using EP testing in that subgroup is of course very tantalizing, in fact we are involved in setting up a study right now to do exactly that. Using a cascade effect of drugs as you suggested two years ago at this meeting. I have no idea how the EP model and the Holter model are going to compare to each other in that particular subgroup. In the patients that are more commonly studied with chronic VPC's, even without triplets, I think practical logistic and expense reasons would warrant not using the EP model in that group who usually require repetitive testing.

Dr. Temple: One can't make the judgements about expanse value, or any of those things without actually looking into the question and really the end point is a mortality end point, so small studies won't get you the answer.

Dr. Morganroth: Unless we use mortality as the end point in the two models a the test criteria.

Dr. Temple: I guess what I mean is to try to reason it out won't work. Nobody can give you an answer as to whether 75% of total and 100% of this o that, no one can answer those questions for you. There is only one crude, boring way to find out. That is to do it.

Dr. Morganroth: That is what we also suggest.

Dr. Temple: What about the possibility that assignment of drugs in some othe way might make people more susceptible to arrhythmias. Most sudden death series have at least a few people who seem to have been put into that situation because of the drug that they were on. Is that another reason to b more inclined to study such testing?

Dr. Morganroth: In my opinion, no, because I am not sure whether inducibilit of a faster ventricular tachycardia is clinically going to correlate with enhanced arrhythmogenesis that has some importance to the patients in terms o more symptoms or more prevalence to sudden death. Again, that is a research question that will have to be ferreted out by doing the comparison study.

Dr. Harrison: I don't really want to deal with the question of electrophysiologic induction as a method for choosing treatment in the really life-threatening patient. That will be addressing later. I sort of have the idea that we are extrapolating from that group of patients which in the past has been pretty non-homogeneous group of patients to this question that Dr. Temple is asking. I don't believe that we have an answer in hand, and he may be right, the only way we are going to find out is do a lot of it in a large group of patients and find out their natural history, but I just have an emotional feeling that is not going to be the way we have to go about this study to show that we could prevent sudden death with antiarrhythmic drugs. In fact, the study may show that we can't prevent sudden death, or we might enhance the likelihood of it with some of the drugs that are available. I don't have the answer, but just from an emotional stand point i don't believe we can extrapolate from the data that are now available with the really life-threatening illness to those patients at this point in time.

Dr. Selby: Considering your experience with stage 1 antiarrhythmic studies, could you tell us if the old method of working out initial human dosage of 1/10 of a dog dose is still valid for antiarrhythmics or do you have a better way of doing it?

Dr. Ehrreich: That is the first time I have heart of that. I don't think there is. Obviously in the different models of arrhythmia you are going to find different sensitivities of the models to the drugs. That is my past experience. Using a fraction of the therapeutic dose is not generally use. At least I haven't done that and I haven't seen anyone else do that. Generally it is the dose extrapolation almost directly from the model in terms of mg/kg, that is the effective dose level and that may vary from model to model. You may choose the lowest dose that is effective in whatever model or the median dose, but there is no rule of thumb at all as far as I know.

Dr. Woosley: That is a very difficult thing to do and trying to select doses, we have often made sure we picked a dose that won't do anything, so you don't try to pick an effective dose for your first dose ranging in man. You pick an ineffective dose, realize that it is likely to be ineffective and work up very slowly and carefully. We have often taken 1/100th of the effective dose in animals if it is guaranteed not to hurt anyone and then move into man with that. Just a comment about the placebo question that came up earlier. I agree with what everyone said earlier about the fact that baseline and placebo were almost always the same in these drug studies, but these are patients selected for their reliability and stability and you even admit that 35% don't agree. I think I agree with the comments about the placebo effect, it is significant in individuals, so I just make a plea to keep the placebo in the studies, just realize that you may not need it.

Dr. Bigger: I agree about the variability, I am not sure it is due to the placebo Ray, because we don't find any more variability when we do two recordings with no placebo than comparing one recording off placebo and one on. We see the same degree of variability and it can be substantial in about a third of the patients. I don't think anyone has really demonstrated effect of placebo convincingly.

Dr. Woosley: We do have individual patients that we have seen marked placebo effects. Patients relax when they start getting some pills and their arrhythmia gets better. They get excited when they get pills and their arrhythmia seems to worsen. They are rare, but they do exist.

Dr. Bigger: I would concede, they almost certainly have to exist, given the fact that arrhythmias respond or don't respond to rate changes, and so forth. That would have to be the case in some subjects, I am sure.

Dr. Ruffy: I would like to hear some strong arguments in favor of the continued need of comparative studies. It seems to me that when we compare a

new drug to a commercially drug, we submit that half of the patients, or that each patient for half of the study to a predictable amount of side effects including sudden cardiac death and to a predictable amount of ineffectiveness. I am not sure that we need to continue these sort of protocols.

Dr. Lipicky: There will be more discussion of that this afternoon, but a brief comment. It turns out that if you look through the history of new antiarrhythmic drugs, it seems that what you are saying is right. They all look the same. That may well be because of the experimental designs that have led to their development. The circumstances that truly differentiate the drugs haven't quite been elucidated. In fact it becomes rather critical I think to have some comparative design, if one has clearly a drug that has antiarrhythmic activity, if it is compared against placebo or in some appropriately historically controlled trial, it seems like it is a relatively critical question in that particular state that is being studied to know how it compares with something that one has a large experience with.

Dr. Temple: If all one wanted to know was , does this drug have any antiarrhythmic activity, the answer is almost surely no. If it is a drug with reasonable activity, you will detect it probably in an uncontrolled study. There are other things that you want to know. I think you do want to know how it compares to drugs that you are familiar in a population that is reasonably well defined and you use the control agent to help define the population so that you can interpret what a 20% response means. It may be if the control agent didn't do any better, you may not need to be quite as discouraged as you thought you were going to have to be. The other thing is that it helps you interpret the side effects that emerge. A given population may have a certain number of deaths or syncopal episodes, and things like that and you really want some control agent to help you interpret that so that you won't just attribute it to the new agent blindly. You may learn something from having the control agent there. There are good reasons, one of which is that you can prevent the premature death of a drug by having a control agent.

Dr. Ruffy: It seems to me that there have been enough of these studies performed that we could establish criteria based on the number of patients that have been put on quinidine over the years in control studies.

Dr. Temple: If someone were to sit down and describe the baseline characteristics of the patients in those trials so that in a very predictable way you could look at a patient as he enters and know what is going to happen to him, then conceivably you could do that, but nobody really has and the results in

different studies come out different suggesting that the people entered even by what look like similar criteria are not as alike as one would have supposed.

Dr. Kupersmith: I just want to ask a technical point about the number of VPC's required to enter a study and before that I just want to say that if you do studies in any number of patients with mitral valve prolapse, you are going to find a very strong placebo effect on arrhythmias. Just the ability of a physician's phone number is often enough to diminish the number of arrhythmias. I would like to ask about the number of VPC's. Most studies now require patients with 30 or more VPC's per hour. It seems to me that if you do large numbers of patients, you could decrease that number. All one would have to do is increase the number of patients. You could also decrease the amount of Holter time by increasing the number of patients and I think this would be beneficial, because we really do studies on very small numbers of patients compared to the number in whom the drug will be given after approval. I wonder what the comment on that would be?

Dr. Lipicky: The hypothesis as you forwarded it is certainly plausible. The question I guess would be whether one could actually show that that is true.

Dr. Bigger: There are two general areas of problems with respect to the question you are asking. One is in the area in the reliability of detection and enumeration of the arrhythmia, where obviously it is easier when the counts are higher and the cost is lower and the level of confidence is greater. That is one area that we have been discussing. The other area is what is the meaning of the ventricular arrhythmia frequency in the terms of the biology of the disease? At what point does it really pose risks, and I was trying to point out this morning, I think there is some disparity in ischemic heart disease between the levels that contribute to risk and by mechanisms we are still not sure of, whether it is intrinsically all due to the V counts themselves or due to the interactions they have with other risk variables. Another very severe problem I was also opening up for discussion. There is one area of the ease of enumeration and the confidence in data in response to treatment, that whole large area. The other large area is the biological meaning of the event itself and what levels pose what risks.

Dr. Lipicky: Just one quick comment and that is that if the only point of the study is to look for differences in VPB rates, whether or not it has biological relevance has no meaning.

Dr. Kupersmith: I think that is the point. That the biological relevance of any of this is undetermined and if you use enough patients, you will make up for a lot of the problems that you have in an individual patient. Even problems of detection.

Dr. Harrison: Certainly when we talk about the biological significance being death, that is what I am going to talk about in talking about sudden death prevention trial with antiarrhythmic drugs this afternoon and I think that there is where I would propose that you use the Bigger criteria of greater than 10 VPC/hr and repetitive forms as the entry criteria in that situation.

THE VALUE OF ELECTROPHYSIOLOGIC TESTING IN PREDICTING LONG-TERM EFFICACY OF ANTIARRHYTHMIC DRUGS IN PATIENTS WITH LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

JEREMY N. RUSKIN, M.D., and HASAN GARAN, M.D.

In recent years, electrophysiologic techniques have played an increasingly important role in the diagnosis and management of patients with life-threatening ventricular arrhythmias. In assessing the value of programmed stimulation techniques in the management of patients with ventricular arrhythmias, the following issues must be addressed: the sensitivity and specificity of programmed electrical stimulation (PES) - induced tachycardias; the safety and practicality of serial pharmacologic-electrophysiologic testing techniques; the reproducibility of responses to antiarrhythmic drugs during serial electrophysiologic testing; and the predictive value of programmed electrical stimulation in selecting long-term antiarrhythmic drug regimens.

The basis upon which electrophysiologic testing techniques is founded is the ability to reproducibly initiate by programmed electrical stimulation putative reentrant ventricular arrhythmias in patients with a history of recurrent ventricular tachycardia or fibrillation. The ability to reproduce these clinical arrhythmias under controlled conditions in the cardiac electrophysiology laboratory provides a reproducible endpoint for assessing the therapeutic and potentially adverse electrophysiologic effects of antiarrhythmic drugs. Preliminary studies in patients with recurrent supraventricular and ventricular tachycardia suggest that prevention by antiarrhythmic drugs of the ability to initiate by programmed electrical stimulation tachycardias that were previously inducible by comparable stimulation techniques (in the absence of antiarrhythmic drugs) was predictive of freedom from recurrent episodes of spontaneous

supraventricular or ventricular tachycardia over short-term follow-up.[1-3] Subsequent studies in larger numbers of patients with recurrent ventricular arrhythmias have documented the predictive value of electrophysiologic testing techniques in selecting long-term antiarrhythmic drug regimens.[4-6]

The sensitivity of programmed electrical stimulation techniques in reproducing sustained ventricular tachycardia in patients with a history of spontaneous, recurrent sustained ventricular tachycardia is relatively high. In the series published to date, ventricular tachycardia has been reproducibly initiated by programmed electrical stimulation in 70 to 90 percent of patients with clinically documented, recurrent sustained ventricular tachycardia.[7,8] In a majority of patients, ventricular tachycardia can be initiated by single (20-35%) or double (45-60%) premature ventricular stimuli delivered during fixed-rate ventricular pacing. In the remaining patients, other modes of stimulation, including triple premature ventricular stimulation during sinus rhythm or ventricular pacing or the delivery of brief bursts of rapid ventricular stimuli, may be required for arrhythmia initiation. In a small percentage of patients, left ventricular stimulation may be required for the initiation of ventricular tachycardia when all modes of stimulation from the right ventricle are ineffective. However, this approach is rarely indicated and is not practical for long-term serial antiarrhythmic drug testing. In another small subset of patients, the use of low-dose isoproterenol infusion may facilitate the induction of ventricular arrhythmias which cannot be initiated by a standard programmed stimulation protocol.

In patients with a clinical history of recurrent, nonsustained ventricular tachycardia, the sensitivity of programmed cardiac stimulation techniques approximates 60 percent in the series reported to date, a figure considerably lower than that observed in patients with sustained ventricular tachycardia.[7,8] In patients with a history of out-of-hospital ventricular fibrillation, it has been our experi-

ence that ventricular tachycardia or ventricular fibrillation can be initiated in approximately 75 percent of patients.[5,9]

The specificity of ventricular tachycardia initiated during programmed ventricular stimulation is extremely high. In two studies reported to date, the specificity of this finding was 98 and 99 percent, respectively.[7,8] It is apparent that the use of more aggressive modes of programmed stimulation, such as triple ventricular premature stimuli delivered during ventricular pacing, will enhance the sensitivity but lower the specificity of induced ventricular arrhythmias in all populations studied.

The desired endpoint of serial electrophysiologic testing is the inability to initiate a tachycardia that is reproducibly inducible in the absence of antiarrhythmic drugs. This endpoint can be achieved in somewhere between 35 and 75 percent of patients studied. This wide range of success rates results from differences in the patient populations studied within different laboratories, as well as major differences in the stimulation protocols employed and in the definitions of a "positive" response. Partial suppression of an arrhythmia, such as a change in the grade of stimulation required to initiate a tachycardia, slowing of the tachycardia rate, or conversion of a sustained tachycardia to a nonsustained tachycardia or one which is more easily terminated than during control studies, are of uncertain prognostic significance. In our experience, a drug-induced increase in the grade of stimulation required to initiate an arrhythmia may have some positive predictive value, but the remaining criteria listed above are of little or no prognostic value with regard to freedom from recurrent arrhythmias. In addition to causing complete or partial suppression of an inducible arrhythmia, an antiarrhythmic drug may exert no effect or may, in some cases, exacerbate an inducible arrhythmia. In our experience, there exists a subset of patients who are more susceptible to both spontaneous and inducible ventricular arrhythmias in the presence of one or more antiarrhythmic drugs than in the absence of antiarrhythmic drugs. It appears

that one of the major advantages of serial electrophysiologic testing may be in detecting these potentially adverse electrophysiologic effects.

The determinants of a successful antiarrhythmic drug regimen are numerous and include: previous drug history (i.e., the number of drugs tested), the degree of underlying left ventricular dysfunction, the definition of ventricular tachycardia suppression, and the stimulation protocol employed. It is evident that patients with a prior history of unresponsiveness to multiple antiarrhythmic drugs are less likely to achieve arrhythmia suppression during serial drug testing than are patients who have no prior history of resistance to antiarrhythmic drugs. The definition of ventricular tachycardia suppression during serial electrophysiologic testing will influence significantly the number of patients in whom "control" is achieved. For example, laboratories in which more aggressive stimulation protocols are applied during serial drug testing than those used during control studies will achieve "complete suppression" of inducible arrhythmias in a substantially smaller percentage of patients than laboratories in which the grade of stimulation required to initiate the arrhythmia during control studies is not exceeded during serial drug testing. Similarly, laboratories which define "complete suppression" as no more than one, two, or three nonstimulated ventricular responses will achieve "suppression" or inducible arrhythmias in a smaller percentage of patients than laboratories which define complete suppression as no more than four nonstimulated ventricular responses. Thus, differences in patient populations, nomenclature, and stimulation protocols between laboratories probably account in large part for the wide range of success rates reported from different laboratories and underscores the need for standardization in the use of these techniques.

The reproducibility of responses to an antiarrhythmic drug during serial electrophysiologic testing is high.[10] We carried out a study in 65 patients in whom complete suppression of an inducible arrhythmia (VT or VF) was achieved

during serial drug testing. In these 65 patients, repeat programmed ventricular stimulation was performed on precisely the same drug regimen one to five days later. No attempt was made to control for the time of day at which these studies were performed. Sixty-one (94%) of 65 patients manifested concordant responses to programmed ventricular stimulation at the time of the second electrophysiologic test on the same antiarrhythmic drug regimen. In 4 patients (6%), discordant responses were observed at the time of the second electrophysiologic test. The presence of inducible ventricular tachycardia at the time of the second test in these 4 patients remains unexplained and was not due to significant variations in plasma drug concentrations or a change in the site or mode of ventricular stimulation.

Several studies have addressed the positive predictive value of electrophysiologic testing in patients with recurrent life-threatening ventricular tachyarrhythmias. In studies involving several hundred patients, the positive predictive value, defined as the percentage of patients in whom complete arrhythmia suppression is achieved during electrophysiologic testing and in whom no spontaneous arrhythmia occurs at one to two years of follow-up, ranges between 80 and 95 percent.[4,6,9,11] The recurrence rate of ventricular tachycardia in patients who are discharged from the hospital on a drug regimen on which ventricular tachycardia is persistently inducible ranges between 40 and 85 percent in the series reported to date. Thus, the positive predictive value of electrophysiologic testing (i.e., suppression of an inducible arrhythmia predicting a successful outcome) is higher than the negative predictive value (i.e., failure to suppress an inducible arrhythmia predicting spontaneous recurrence of the arrhythmia). Recent observations reported by Swerdlow et al have shown that, in patients with a history of life-threatening ventricular arrhythmias, the two most powerful independent predictors of freedom from sudden cardiac death are the degree of congestive heart failure as defined by the New York Heart Association classification, and the presence

of an effective antiarrhythmic drug regimen as defined by electrophysiologic testing.[11] Of major importance is the fact that these two variables were both powerful and independent predictors of outcome in this patient population.

In recent years, it has become apparent that antiarrhythmic drugs may exert a variety of unfavorable electrophysiologic effects in patients with recurrent ventricular arrhythmias. These effects include facilitation of induction of an arrhythmia, acceleration of the tachycardia rate, conversion from nonsustained to sustained ventricular tachycardia or ventricular fibrillation, and induction of "nonclinical" forms of ventricular tachycardia. These adverse effects are observed commonly in the electrophysiology laboratory during serial antiarrhythmic drug testing. The precise clinical relevance of these effects is yet to be defined. However, it has been our experience that occasional patients manifest both spontaneous and inducible ventricular tachycardia in the presence of an antiarrhythmic drug and manifest no evidence of inducible ventricular tachycardia in the absence of that drug.[5] In this subgroup of patients, we have elected to discontinue antiarrhythmic drug therapy and have observed no recurrent arrhythmias in any individual in whom electrical initiation of the arrhythmia could be achieved only in the presence of antiarrhythmic drugs.

The complications associated with intracardiac electrophysiologic procedures are comparable to those observed with other cardiac catheterization procedures.[12] In our experience, we have observed no procedure-related fatalities and an overall complication rate of 2 percent. A majority of these complications are thromboembolic in nature, although a small incidence of local and systemic infection as well as pneumothorax have been observed. The role of systemic anticoagulation in preventing thromboembolic complications during electrophysiologic procedures is yet to be defined in a prospective trial.

In summary, electrophysiologic testing procedures are both sensitive and specific when applied to patients with a

history of recurrent, sustained ventricular tachycardia. The technique is also sensitive when applied to patients surviving an episode of out-of-hospital ventricular fibrillation, although the specificity of induced nonsustained ventricular tachycardia as well as induced ventricular fibrillation is not well defined. Serial electrophysiologic testing techniques accurately predict the outcome of long-term antiarrhythmic drug therapy in these patient populations. In addition, these techniques are useful in detecting the adverse electrophysiologic effects of antiarrhythmic drugs in patients in whom one or more of these agents may be arrhythmogenic.

Despite these advantages, several important questions regarding the use of electrophysiologic techniques are yet to be answered. For example, the duration of the predictive value of electrophysiologic testing is yet to be defined. The incidence and significance of so-called "nonclinical" tachycardias remains unknown. The classification and significance of induced nonsustained ventricular tachycardias as well as their specificity in patients with structural heart disease also remains to be defined. The value of electrophysiologic techniques in selecting patients at risk for but who have not yet experienced a potentially life-threatening arrhythmia is just beginning to be explored. Finally, problems of standardization exist among different laboratories with regard to the types of programmed stimulation protocols employed, the types of antiarrhythmic drugs used, and the protocols under which these drugs are administered and tested. Furthermore, standardization of the definitions of complete, partial, and non-suppression of arrhythmias during electrophysiologic testing as well as the nomenclature applied to various types of tachycardias (e.g., repetitive responses, nonsustained VT, and sustained VT) is required if the combined experiences of different laboratories are to be used productively.

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EFFICACY MODELS: ACUTE VENTRICULAR ARRHYTHMIAS

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What are the appropriate therapeutic endpoints toward which therapy for acute ventricular arrhythmias should be directed? Is suppression of spontaneous ventricular ectopy although it is asymptomatic sufficient to assure protection against the recurrence of symptomatic ventricular tachyarrhythmias? Is reproduction of life-threatening arrhythmia by electrophysiologic testing required to evaluate the efficacy of therapeutic regimens for patients with ventricular tachyarrhythmias? These questions must be answered as we evolve the correct approach to the treatment of patients with life-threatening ventricular tachyarrhythmias. In the consideration of which drugs are effective there is an implicit assumption made that we know how to evaluate what is appropriate and correct therapy; however, this issue is probably more in question than the efficacy of specific drugs and devices. Not only must we consider the capabilities of the various techniques to identify the correct regimen but we must also consider the technical expertise and cost involved.

The concept that suppression of spontaneous ventricular arrhythmias whether symptomatic or not is sufficient to define efficacy when treating sustained ventricular tachycardia or fibrillation is based on epidemiologic data which show an association between these two types of arrhythmia and clinical reports which suggest this approach is effective. On the other hand, electrophysiologic testing using programmed electrical stimulation has been proposed as the method of choice in selecting antiarrhythmic therapy in patients with recurrent symptomatic ventricular tachyarrhythmias because such testing prospectively assesses the effect of drug regimens on the inducibility of the arrhythmia (i.e. the arrhythmogenic

potential of the ventricle). Several clinical studies have also suggested that this approach is effective.

In the evaluation of how one should design studies to assess efficacy of treatment regimens in acute ventricular arrhythmias, it is imperative that a consideration must be made of which technique should be used or if a combination of the two approaches would be most effective.

A LOOK TO THE FUTURE: OUTPATIENT PLACEBO CONTROLLED TRIALS OF ANTIARRHYTHMIC DRUG EFFICACY IN PATIENTS WITH LIFE THREATENING VENTRICULAR ARRHYTHMIAS

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During the past decade increasing numbers of patients who have survived an episode of out-of-hospital sudden death or have recurrent episodes of sustained ventricular tachycardia requiring pharmacologic or electrical conversion have been referred to major medical centers. The rapid development of a large number of new antiarrhythmic compounds, improved methods of ECG monitoring, intracardiac electrophysiologic techniques for testing antiarrhythmic drug efficacy and a variety of surgical procedures have increased the number of therapeutic options available for such patients. Despite these apparent advances in management, our observations over the past five years in treating over 300 such patients suggest a relatively poor outlook for many of these patients. This manuscript deals with some of the limitations and shortcomings of currently available treatment modalities.

In the late 1970's intracardiac electrophysiologic studies became popular for determining antiarrhythmic drug efficacy for patients with serious life threatening ventricular arrhythmias One of the early promises of this technique was that by rapidly screening a number of intravenous drugs one could quickly reject ineffective drugs and identify the best antiarrhythmic regimen for a given patient. Most drugs in widespread use at the time had relatively short half-lives, and even when oral loading was necessary it could be accomplished in a matter of a few days. Thus, the technique initially shortened the required hospital stay for patients with life threatening arrhythmias. Recently, however, the duration of hospitalizations for patients with recurrent ventricular tachycardia or fibrillation have become unacceptably long. A variety of circumstances

contribute to this problem. These include the fact that many newer drugs such as amiodarone and lorcainide have considerably longer half-lives and may require one week to one month to come to steady state. Furthermore, with increased appreciation of the role of active drug metabolites and the unavailability of some drugs in an intravenous preparation there has been an increasing need to perform electrophysiologic testing of oral rather than intravenous antiarrhythmic therapy. Finally, many drugs must usually be tested in a single patient before an effective one is found. Not only do these patients have prolonged hospitalizations but the treatment is psychologically draining for the patients and physically demanding for their physicians. The major justification for these prolonged hospitalizations and repeated intracardiac electrophysiologic tests is that we cannot afford to make a mistake with therapy since the patient may not survive an arrhythmia recurrence.

In early studies reporting the value of intracardiac electrophysiologic studies, effective antiarrhythmic drug therapy was found in 70 to 80% of patients. More recently, however, effective drugs have been found in only a minority of patients with recurrent sustained ventricular tachycardia or fibrillation. At the present time our overall rate of successful testing in over 300 patients is about 35%. The reasons for this decline in the incidence of drug efficacy are unclear. Referred patients may be more critically ill and may be more drug resistant than those seen previously. Additionally more stressful methods of testing are being used, such as three ventricular premature stimuli rather than two ventricular premature stimuli (2). Thus our testing method may be excessive and demand more of a drug than is clinically necessary. Unfortunately, however, is is not feasible to eliminate use of three premature stimuli since a large portion of patients require this for induction of their clinical arrhythmia in the baseline state.

In recent years amiodarone has achieved considerable notariety as an antiarrhythmic agent. Initial reports from Europe were encouraging; virtually all arrhythmias were

controlled on low doses of 200 to 400 mg daily with few side effects. Widespread clinical experience in patients with life threatening ventricular arrhythmias in this country has demonstrated that higher doses are required to control these serious arrhythmias and that a considerable price in drug toxicity is paid. In our series nearly 10% of patients have experienced pulmonary fibrosis and by two years over 20% have been withdrawn from amiodarone therapy because of side effects. It has been widely accepted that intracardiac electrophysiologic testing may not be predictive of long-term efficacy or inefficacy of amiodarone. In our series of 77 patients with life threatening ventricular arrhythmias only 30% continue effectively treated at two years, and 10% have had cardiac arrests. While there can be little doubt that amiodarone is an excellent antiarrhythmic drug, it is not the ultimate answer to control of life threatening arrhythmias.

Although early reports of surgical therapy guided by endocardial mapping and resection were promising, our experience has been less than optimal. Many patients are not candidates for endocardial mapping and resection because their underlying rhythm is unmappable ventricular fibrillation or polymorphic ventricular tachycardia. In addition some patients have multiple induced morphologies which makes intraoperative mapping difficult. In addition, the arrhythmia mechanism is not always clarified by mapping. A large number of patients have poor left ventricular function which places them at an unacceptably high surgical risk. Including emergency operations the immediate operative mortality ranges from 10 to 20%. Given this high operative mortality it is hard to justify surgical therapy for a patient who has experienced only a single episode of sudden death, patients with rare ventricular tachycardia recurrences, or patients with poor left ventricular performance.

Another major disappointment is that some patients whose VT is rendered uninducible by an antiarrhythmic drug still may die suddenly (3). Additional patients will ultimately succumb to progressive left ventricular dysfunction, subsequent

myocardial infarction or other nonarrhythmic catastrophes. The reasons for these sudden deaths in patients taking apparently effective drugs may be change in underlying cardiovascular disease, true drug failures or noncompliance by the patient. The majority of our sudden deaths in patients discharged on a drug which rendered their ventricular tachycardia or fibrillation uninducible occurred either when they spontaneously discontinued their medication against advice or after side effects forced a reduction in dosage.

Because a beneficial drug can only be found in approximately one-third of patients with life threatening ventricular arrhythmias, it would be advantageous to be able to select those patients likely to benefit from serial electrophysiologic drug testing and to move on to surgical or other modalities of therapy in those patients unlikely to benefit. Recent experiences at Stanford indicate that it is possible to identify those patients for whom electrophysiologic testing is likely to find an effective drug (4). Using multiple clinical features the probability of finding a successful drug may be predicted for individual patients. Factors identifying a high likelihood of successful drug testing are absence of structural heart disease, female sex, absence of ventricular aneurysm, and number of empiric antiarrhythmic drug trials previously failed.

Given the observations that there is a high rate of drug failure, that effective drugs can be found in only a minority of patients, and that many patients are not good candidates for surgery, it seems logical to consider the implantation of automatic defibrillators (or cardioverters) in many of these patients. Recent experience indicates that these devices can sense and terminate ventricular tachycardia and fibrillation reliably. Soon an electrocardiographic record of each arrhythmic episode will be available to document arrhythmia occurrence and appropriate sensing and termination by the device. Although major surgery is required for implantation and to date only a relatively small number of patients have been treated, enthusiasm for these devices is increasing rapidly. If they prove to be safe and reliable, one can make

a strong case for early implantation of such a device in all patients with ventricular tachycardia and fibrillation whose clinical features indicate that they are unlikely to benefit from serial electrophysiologic study and who are poor operative candidates. In addition, one could justify the use of implanted cardioverters or defibrillators in those patients who have experienced only a single cardiac arrest who have a 30% risk of recurrence over the next 12 to 18 months.

Once a patient has an implanted defibrillator or cardioverter our approach to the patient can change. Consider the possibility that we might no longer be burdened by the fear of selecting an ineffective antiarrhythmic drug. This might shorten hospitalization and reduce the need for serial electrophysiologic drug testing. Outpatient empiric drug trials could even be considered for patients whose arrhythmic episodes were relatively infrequent. Placebo controlled or randomized drug trials might even become possible. The incorporation in the implanted device of internal memory and telemetry data transmission would provide objective assessment of drug efficacy. Perhaps for the first time we could perform truly controlled trials in patients with acute, life threatening ventricular arrhythmias. While this scenario is hypothetical, perhaps it merits consideration.

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Dr. Gentzkow: Could the relatively low rate of success in preventing VT during EP testing that Dr. Winkle's data showed for investigational agents be because they are tested in patients who are already resistant to other drugs and therefore are less responsive in general. That is the custom, that indeed we only expose patients who are resistant to conventional agents to investiga tional drugs. Do you think it is feasible, practical, and ethical in fact, once some of these newer agents are proven to be more effective in suppressin PVC's than standard agents, to test them in patients who have not been shown to be resistant to conventional agents. Perhaps this can be done in a random way, so that we can get some feeling for relative efficacy in the EP setting between investigational drugs and "standard agents"?

Dr. Ruskin: Yes. I think with one caveat, and that is that the drug should have some potential advantages over other available agents, such as a desirable safety profile, an acceptable half life such that it might be more convenient to dose with that drug than with procainamide and those sorts of things. I think that with the safety established and desirable kinetic available data that that is a rational and ethical thing to do.

Dr. Scheinman: We have learned a tremendous amount with amiodarone and our data is identical to that of Dr. Winkle - only about 10% of the time will ventricular tachycardia become non-inducible during EP testing after prolonge therapy with oral amiodarone. Nevertheless amiodarone in our experience is 75% effective over two years. It is certainly the most effective agent that we have. If you are going to use drugs like flecanide and encainide, I think it is very reasonable to test them in that way. I think you have to define what your end points are. It may be that inducibility in the laboratory is not the proper end point. You have to follow the patient and find out whethe

the efficacy of the newer drugs will in fact be predictable from the EP testing or whether they will turn out to be more like amiodarone.

Dr. Lipicky: It appears to me that electrophysiological testing is a way of defining how a drug should be used. Such testing shows how to pick the drug, as opposed to establishing that a drug has efficacy in a particular clinical state and that those are two really very different things.

Dr. Reid: Would it be reasonable to submit an NDA in which most of the support were claims of efficacy of a new antiarrhythmic agent based entirely upon the results of programmed stimulation?

Dr. Lipicky: No.

Dr. Bigger: That is the patients that while with regard to Dr. Ruskin's study of patients who had cardiac arrest on antiarrhythmic drugs, who were not inducible in EP testing off of the drugs and were inducible when placed back on them. Do you have any idea, any kind of data that would allow you to give some estimate about the number of people at risk of antiarrhythmic drug caused cardiac arrest. That is, what proportion of these patients on these drugs who show that abnormal response? Have these observations changed your practice in any way, or caused you to make any recommendation, such as, in patients who have ischemic heart disease, a scar in the ventricle and poor left ventricular function and have an event that may be life threatening, such as runs of PVC's. Should they be considered for EP testing or not?

Dr. Ruskin: I can't give you an accurate answer. I will speculate. We are in a state of informed bewilderment about this particular issue. We have made some observations and I think several other people have as well that are frightening, but we don't know either the numerator or the denominator. In our series, there were 6 of 97 patients in whom we were reasonably sure that the antiarrhythmic drug that they were taking at the time of the arrest was intimately involved with their arrest. I think we proved that in 4 of the 6

with electrophysiologic testing. If one were to be extremely conservative about it, I would have to say that in our series it is about 4% of the overall group of patients resuscitated from pre-hospital arrest unassociated with acute infarction. I think that is an unfair thing to do though, because it is such a biased population and such a select subgroup by virtue of all the steps in between that take place, from collapse until they get to a tertiary center, that we just don't know the answer to the question. What to do with the information? The answer is again, I don't know, except that if there is a way to develop mechanisms by which we can become more aware of adverse effects such as electrical stimulation or even holter monitoring. I think the statistics from Lown's group on adverse effects are really quite similar to what we have seen with programmed stimulation that they ought to be utilized and compared. I don't think we can make any recommendations about how it should influence practice until we know what the predictive value of those techniques are in actually proving that a drug is going to be harmful to a patient and I would be loathe to make any recommendations at this point because I just can't base it on fact.

Dr. Scheinman: Suppose you are thinking about using quinidine in a patient who has an old infarct, do you bring them in the hospital and monitor them?

Dr. Bigger: Yes.

Dr. Scheinman: Is that for all patients with organic disease who are being put on type I drugs?

Dr. Bigger: Yes, with poor left ventricular function and scar in the ventricle, yes.

Dr. Scheinman: Then you probably have the best data on the numerator. How often do you see real problems monitoring them?

Dr. Bigger: For short periods, it is relatively rare, between 5 to 8%.The second question I had had to do with the factor I think is causing the waning

of enthusiasm for amiodarone, which I think is caused by serious, often lethal pulmonary complications, occuring in 7 to 10% of the patients and about half those being fatal. Perhaps it is seen more in this country and in this group of patients because the doses used are higher than have been used in Europe or used in supraventricular arrhythmias and I wonder if you have any data.

Dr. Winkle: I think that may be true, because we have not seen it in any of a smaller number, about 20 or so, patients treated with atrial arrhythmias with much smaller doses. The problem in the VT patients is that it is very hard to reduce the dose down to the same level that you can treat ventricular arrhythmias with. While it may be a true statement, I am not sure clinically how relevant it may be for these patients. We in fact do have one patient who developed fairly severe symptomatic amiodarone pulmonary toxicity after the drug had been withdrawn for a couple of weeks. It cleared and he was treated successfully on lower doses.

Dr. Horowitz: I would like to ask Dr. Campbell who may have a different perspective on that particular question to address it also.

Dr. Campbell: The European experience related to dosing and pulmonary fibrosis would suggest that there is a relationship. That is, those that are taking larger doses are the ones who show pulmonary complications. One piece of information about amiodarone that is relatively new, is the tissue levels of the drug both the active drug amiodarone and its metabolite desethyl amiodarone in various organs and it seemed to be concentrated particularly in those organs which showed toxic features. This has certainly led in Europe to a keen reduction to the minimum level of drug that is compatible with effect. It is too soon to say whether that will reduce the other complications or whether it will influence pulmonary fibrosis. The U.K. incidence of pulmonary fibrosis is approximately .6 to .9% of those taking amiodarone and the average dose is between 200 and 400 mg/day.

Dr. Horowitz: I would also like to add that in the last 18 months we have been using a regimen virtually identical to that which Dr. Campbell described and the incidence of side effects both acute and chronic appear to be considerably lower that we preveiously encountered with higher doses.

Dr. Ruskin: We have seen 4 cases of well documented pulmonary fibrosis in 3 of the 4 patients were taking either 200 or 400 mg a day. I think that a low dose doesn't guarantee immunity from the problem, but it may in part be related to duration of therapy as well as dose because I think the drug probably continues to accumulate for long long periods of time.

Dr. Ruffy: Oncologists when they have to treat leukemia or other forms of cancer know that they have to use multiple drugs in order to be successful. I think one of the things that is lost in new drug trials is the virtue of combination of drugs. I think we all share Dr. Winkle's pessimism when it comes to controlling a malignant ventricular arrhythmia with a single drug. We have a very low success rate. It may not be the case when you go to combinations and one of the advantages we have now with the vast number of new drugs available is that they have different electrophysiologic properties and side effects. I wonder how the panelists would feel about early introduction of combination drug protocols trying to select drugs that are known to be compatible at least on a theoretical basis?

Dr. Winkle: When David Ross was at Stanford, he looked at our experience with drug combinations in the electrophysiology lab. By and large people were not treated long term with combination regimens because virtually all drugs that had been tested singly and failed, to prevent ventricular tachycardia when tested then in combination, also failed. However I know that this is not the experience of other people. I think in fact Dr. Ruskin has had a lot of experience using mexilitine with other drugs.

Dr. Ruskin: We haven't addressed the problem in any prospective or rigorous way. We use combinations when single agents don't work and I think sometimes a so-called type I drug with another drug of the mexiletine-tocainide group might be effective but it has not bailed us out nearly as frequently as we would have hoped. I think it can be useful, but it doesn't really solve the problem.

Dr. Horowitz: Does anyone see an overriding rationale for combining drugs of different groups. I think everyone has the same impression that it is not the magic potion, but is there at least some theoretical reason to suggest or to imply at least that combinations should be effective, whether they turn out to be or not.

Dr. Scheinman: I don't think so. You could probably find a nimble cellular electrophysiologist who would give you very good reasons for doing this, but in fact if you look at the clinical literature, there really isn't very much critical data that suggests that combination therapy works and I think both the experience at the Hospital of the University of Pennsylvania and Stanford is such that at least when you can rigidly control things in the laboratory, combinations don't work.

Dr. Horowitz: I think the only combination that has been well reported in the literature is the combination of a beta blocking drug with other antiarrhythmic drug? There are a number of reports which suggest that this combination may be effective. I have personally not seen that. There is probably insufficient data to suggest any other combination is effective frequently

Dr.Campbell: I wonder if part of the problem is the fact that the nimble minded cellular electrophysiologist would make a basis for combination therapy on scientific terms. I think one of the great difficulties in clinical practice is that we choose our therapies empirically. In the U.K. we have a

number of agents available, unfortunately, after trying one, the next available agent is very much a matter of personal choice and we certainly don't have the evidence to say that if a patient responds in one or another other way to a class I antiarrhythmic agent, the next drug tried should be another class I or a class II or whatever. I think until we tackle the question of how we should use and incorporate multiple agents, I don't think we can answer those questions.

Dr. Griffin: I was very interested to hear Dr. Winkle's comments on the use of the implantable defibrillator in conjunction with drug therapy, rather than as a primary therapy. There are also a number of devices on the market, which might allow serial long-term, non-invasive electrophysiologic testing. I was curious to know what the panel's comments would be on the role of such devices in patients with sustained ventricular tachycardia which might not necessarily result in syncope or sudden death.

Dr. Winkle: I think that is a very good idea, because most of our VT patients are coming back to the lab 4 and 5 times. Some people leave catheters in and others put them in every time, and then oftentimes, a year later, the patient has a drug failure and have to come back. I think it is not a bad idea to put in a radio frequency pacemaker that can be hooked up to a stimulator for such studies.

Dr. Ruskin: I think if one views it in terms of defining therapy, it can be very helpful in selected subgroups, but we are not talking about anything that offers any therapeutic benefit in patients in whom you have decided drug therapy offers a long term option. I think it becomes particularly attractive in that subset of patients who require permanent pacemakers, because then you have a real justification for putting in a VVI unit that is also capable of doing stimulation non-invasively. I think that is probably the best sub-set to start with, but I think it is an interesting idea.

Dr. Horowitz: When do you decide the break even point comes? How do you know after the initial study, whether the next drug study is going to be successful or not? I think we would all agree, or at least it would be very feasible, if you knew you were going to have to do 10 drugs studies, that probably putting in the permanent unit makes sense, but at what point do you decide to put it in?

Dr. Ruskin: I think that is an impossible question to answer and your point is well taken. What I was referring to really was the fact that we don't really know the duration of the predictive value of testing in patients in whom we have achieved suppression. We also don't forsee very often the kinds of problems with individual agents that we think are going to be effective.

Dr. Somberg: We have seen a rise of enthusiasm for EP testing and some very effective things done with it in labs around the country and an improvement in mortality. But still, are we going to establish a double standard, when we compare it to the conventional means of trial and error therapy where patients are placed on drugs and the arrhythmias will recur. If you are addressing the approval process for an antiarrhythmic agent, would that not be the way to go 1982-1983, to take the best techniques available, combining Holter monitoring, looking at triggering mechanism and looking at threshold through EP testing and a drug development program, based on those two things with tremendous emphasis, instead of evaluating a drug by seeing reduction of stable PVC's. Personally, I would go with the vigorous EP and Holter approach and not look for tomorrow's science fiction or yesterday's previous methodologies.

Dr. Lipicky: It still seems to me that EP testing is predominantly oriented as a decision maker with respect in how to use an antiarrhythmic drug in a very specific clinical situation; namely those people with serious arrhythmias and in the prevention of sudden death. There appears as best as I can sense it some debate as to whether or not that is an acceptable end point at this

stage and whether or not that really is so or not. Therefore, as a single criterion of demonstrating antiarrhythmic drug activity, that single positive finding, that is that the drug would prevent inducibility in that setting would be insufficient to establish antiarrhytmic activity. On the other hand it would seem to me that any drug that is being developed in today's climate, that the answer to that question must be known. That is, does it or doesn't it, in pretty much the same way as one would expect one to know whether a dru changes ECG intervals or alters hemodynamics or blood pressure. It is a parameter that one needs to contend with and needs to know the answer to. Probably more significant than that is that there really ought to be fundamental information with respect to the drug as to what its dose response relationships are not only as an antiarrhythmic but with respect to all of th potential side effects unless in fact it turns out there are some strange things that occur such as pulmonary fibrosis for example.

Dr. Winkle: I think each of these patient populations serves a different purpose in my mind. I think the types of very sophisticated, elegant, clinical pharmacologic studies, that Dr.Woosley talked about this morning are crucial to the proper clinical use of these drugs. I think that from the therapeutic patient benefit standpoint, the VT patient with programmed stimulation, and intensive Holtering is most relevant for demonstrating drug efficacy, but those are usually very sick patients and another very important aspect of the approval process, is drug safety. I think the stable ventricular arrhythmia patient population does provide an opportunity to stud large numbers of patients to look for toxicity and I think it is being done i a situation where we can probably ethically justify treating these patients based on some of the observations of Dr. Lown and others that perhaps treatin these arrhythmias may in fact be beneficial. There are very few studies showing it is harmful. There may be a number showing no benefit in terms of

long term outcome , but I think the safety aspect of the information derived from these studies is very crucial.

Dr. Woosley: I would like to say a few things about antiarrhythmic drug combinations. Hank Duff and Dan Rodin in our group pulled together our experience at one point it was 17 patients with refractory VT who were resistant to quinidine and other drugs and did not have an adequate response to mexiletine. 15 of the 17 patients had a dramatic response to a lower dose of mexilitine and a lower dose of quinidine with far fewer side effects with either drug alone. One of the things that Hank noticed, and the reason I bring this up was that there were some hints that the electrophysiology may tell us about the efficacy of antiarrhythmic combinations. One of the things that Hank noticed was that the QT was prolonged by quinidine, but when mexilitine was added to the patients, the QT shortened. He then went to Langendorf hearts looking at monophasic action potential duration and conduction velocity and QRS and he found the same thing, that quinidine was slowing conduction and that mexilitine was shortening repolarization. The net effect was a marked increase in ERP to APD ratio. This is preliminary observations in an animal model, but a very dramatic response of that combination in a very sick patient population. People who have now been on the drug combination for 2 to 4 years in every case, so a very refractory arrhythmia controlled with a nice combination that is very well tolerated long term.

Dr. Scheinman: I would like to speak to some of Dr. Winkle's pessimism and throw out a couple of thoughts. In fact, those of us who are doing EP studies I think are finding that the hospitalization doesn't have to be as long as it used to be. The vast majority of patients who don't respond to procainamide are unlikely to respond to other conventional drugs or combinations. All the time that we wasted before in testing drug after drug is not necessary and we

either go to amiodarone or to other experimental drugs, so in my way of thinking, we have actually made things a lot easier. If you have a patient who proves refractory to other drugs and you are deciding whether to put him on amiodarone with all its complications versus whether to put in one of thes permanent defibrillators,do you consider life with a permanent defibrillator normal life? The machine has to wait 15,20,25 seconds before it is sure that it is VF and then it discharges. By that time the patient may have had a syncopal episode or a seizure. You certainly are not going to allow that patient to drive.

Dr. Winkle: Your first point is fully in agreement with the point that I was trying to make that we can identify ways of picking out the patients who will do well or poorly or whether we should more quickly to experimental drugs and I think that will help. The second point is that life on amiodarone isn't normal either. People come staggering into our clinic and it takes a couple of weeks until we lower the dose and I don't know how their driving reflexes are, but in fact, very few people have VF that they go out with instantly. I fact the response time for the automatic implantable defibrillator, the average is about 5.5 to 6 seconds and then it takes another 7 seconds to charge up, so we are talking about 13 seconds. Most people with even rapid V do not lose consciousness during that time. The patients with pure VF during that time will but at least they come back and say I fell down and had a seizure, and you don't get a call saying they died. I agree it is a problem, but I don't think life is that abnormal. Life on these drugs isn't that pleasant either.

Dr. Copen: We have talked for the most part about finding drugs to treat people who have one documented or more than one documented life threatening arrhythmia. In actual fact what we really want is to find drugs that prevent sudden death in the people who are at high risk and have not had that

arrhythmia yet. There has been a fair amount of talk recently about using electrophysiologic testing to identify that high risk group and the medication they should take. I would like to ask the panelists if they think we could extend it to that and whether they think a large volume of laboratories can do electrophysiologic testing as safely as Dr. Ruskin has done it?

Dr. Ruskin: I don't think there is sufficient data at this point to recommend studying patients at high risk, for example post MI patients except in rigorously defined prospective protocols. I for one would find it deplorable if we took away from the two preliminary or primary studies that have been done, the conclusion that everybody potentially at high risk for sudden death should have EP testing and then have drugs selected based on that. I just don't think that data is in yet.

Dr. Winkle: You not only have to show the technique is useful , but you have to show it is better than what Dr. Bigger can do with an exercise test and a holter monitor and some assesment of LV function. I think he can do a very good job in separating high risk and low risk patients. It is more than whether it is predictive, it is whether it is better than we have now.

PROTOCOL DESIGN FOR SUDDEN DEATH PREVENTION

DONALD C. HARRISON, M.D.

INTRODUCTION:

Clinical trials and their interpretation are fraught with difficulties and the possibility of misunderstanding (1-4). An example of a clinical trial which was developed with a number of assumptions based on historical perspective which led to a design that failed to prove the hypothesis which was advanced is that of the multiple risk factor intervention trial recently reported (1). In any trial in which death is used as an end point for the comparison of clinical interventions a number of potential problems exist. It is essential to recognize that death may be due to a series of interrelated phenomena. Some of these may reduce the likelihood of death while others may enhance it. Death itself may result not from the basic process but from another of other possible disease causes, particularly in the age group in which such clinical trials are generally carried out. For our considerations relating to sudden cardiac death the basic process of atherosclerosis may progress, may regress and may remain stable. Its relationship to sudden cardiac death is influenced by the central nervous system, by the autonomic nervous system and frequently by other pharmacologic interventions not directly in the scope of the trial in patients with disease. While sudden cardiac death is a major manifestation of coronary heart disease, it is also the final end result in cardiomyopathies and congestive heart failure due to other causes (5).

In order for us to consider the problem of study design we must define our terms as specifically as possible. For my discussion sudden death will be deaths occurring within twenty-four hours of a primary event whether or not a patient is hospitalized. Instantaneous death or arrhythmic deaths will be defined as deaths occurring within sixty minutes of the event. For my particular presentation I will limit the discussion of sudden death due to coronary artery disease as its clinical course is affected by drug intervention. Although a number of studies to limit antiarrhythmic deaths with the administration of antiarrhythmic agents in this patient population have been attempted (6-11), no clear answers have emerged. On the other hand, definitive answers are available for the beta adrenergic blocking

drugs in the patient with coronary artery disease in the one to four year period following acute myocardial infarction (12-14).

CONSIDERATIONS IN PROTOCOL DESIGN:

Several factors such as patient selection, the biostatistical techniques to be employed, moral and ethical considerations, specific drugs to be utilized and methods for measuring other end points in addition to sudden death must be considered in protocol design.

PATIENT SELECTION:

In order to improve the likelihood of success, selection of patients with increased risk for sudden cardiac death is essential. A number of previous studies have defined the group most likely to have sudden cardiac death as those suffering from acute myocardial infarction (15-22). The likelihood of sudden death is increased greatly within the first six to nine months after infarction. Those patients having both decreased left ventricular function and the occurrence of frequent and complex ventricular arrhythmias have a higher likelihood of sudden death. It seems likely that a subgroup of patients having a prevalence of sudden death approximating 30% in one year can be selected among this group (22). It is in this group I believe studies should be carried out to prevent sudden cardiac death using Class I antiarrhythmic agents. I have previously reported a hypothetical schema for managing all post-myocardial infarction patients. This schema is outlined in Figure 1 and demonstrates that approximately 20% of all patients suffering from acute myocardial infarction might be considered to be in the high risk group and, thereby, candidates for such studies.

Patients age 40 to 75 should be included for study seven days after acute myocardial infarction. Patients with decreased ventricular function evaluated clinically or with radionuclide studies and having ventricular premature beats of greater than twenty per hour on an average over a twenty-four hour period together with at least one complex form represented by multiform beats, short bursts of three or more consecutive ectopic beats, or sustained ventricular tachycardia should be included. Assignment to treatment programs should be made by acceptable statistical techniques (23,24).

SELECTION OF DRUGS FOR STUDY:

Beta blocking drugs have already been used in those patients without contraindications to reduce the likelihood of cardiac death, particularly sudden cardiac death in post-myocardial infarction patients (12-14). A number of reports have documented their effectiveness. It seems unlikely that any study design will be able to omit beta blocking drugs being administered in patients who do not have major

contraindications such as heart failure during the period in which other drugs are administered. Therefore, patients receiving beta blocking drugs should be utilized based on physician choice and stratification performed at a later time for analysis.

Based on isolated cell studies with microelectrodes, electrophysiologic studies, and ECG measurements, I have proposed a modified classification of antiarrhythmic agents in the Vaughn-Williams Class I grouping (Table 1) (37,38). While this schema has yet to be tested clinically it can be used to design a trial of the type we are discussing. Since side effects requiring discontinuing drug administration are common with all of these agents and all are known to have arrhythmogenic potential in some patients, I believe a cascade of drugs in two of the subgroups in my classification represent the best choice at this time. I propose a comparison of the effectiveness of Class IA and Class IC agents in a randomized design. End points for changing to a drug lower in the cascade should be established based upon patient tolerance, the lack of effectiveness and any arrhythmogenic potential for a particular agent.

TABLE 1.

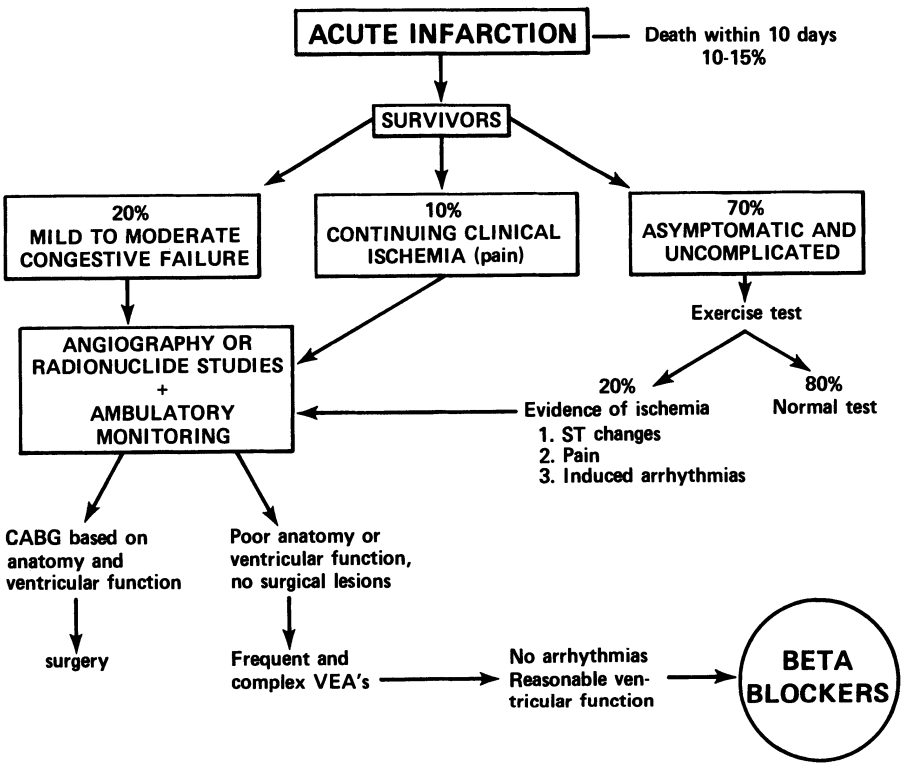


TABLE I. CLASS I DRUGS FOR VEA TREATMENT

CLASS IA:	QUINIDINE	2+ dV/dt ↓, 3+ ↑
	PROCAINAMIDE	ACTION POTENTIAL
	DISOPYRAMIDE	AND QT INTERVAL
CLASS IB:	TOCAINIDE	0-1+ dV/dt ↓, SHORTENED
	LIDOCAINE	ACTION POTENTIAL AND
	MEXILETINE	QT INTERVAL
	APRINDINE	
CLASS IC:	ENCAINIDE	4+ dV/dt ↓, 1+↑ ACTION
	FLECAINIDE	POTENTIAL, WIDENED QRS
	LORCAINIDE	AND ↑ HV

Dosing tiers could be established for each agent to be certain that the patient had achieved a preset plasma concentration of the choice agent. Effectiveness can be determined by the techniques described below at the next ambulatory monitoring for an individual patient. This will permit later correlation of plasma concentration with effectiveness based upon the primary end point of death and upon the measurement of antiarrhythmic effect.

BIOSTATISTICAL CONSIDERATIONS:

A number of biostatistical considerations have been made in planning trials of this type. These include: techniques for determining sample size, for determining the absence or presence of a particular end point (25-26), techniques for stratifying patient groups using single variant and multivariant analysis based upon previously reported data (23,24) and when to stop the trial based on continuous evaluation of the data at intervals after commencing treatment programs (30). Most importantly, one must carefully consider techniques to determine effective drug programs for suppression of arrhythmias if this is to be a secondary end point . Since spontaneous variability of arrhythmias in these patients is so common, controversy about the preferred method for demonstrating antiarrhythmic activity has developed (31-36).

At our institution a number of approaches to documenting reduction in ventricular arrhythmias has been studied (33, 35, 36). I wish to present only the method of Sami (35,36) which would suggest that all patients should have ambulatory monitoring on at least two occasions prior to being commenced on antiarrhythmic drugs (Figure 2). Computer analysis of the ambulatory recordings should be possible. Standard statistical techniques for this type of analysis with the establishment of confidence intervals and a comparison of response at 3, 6, 12 and 24 months after commencing the primary agent should be made (Figure 2 and 3).

Other approaches rather than monitoring may be considered to document

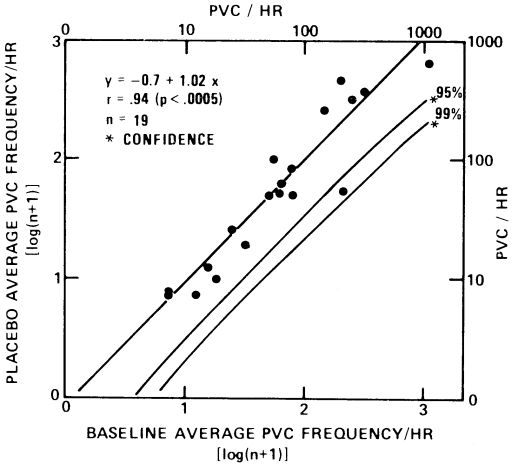
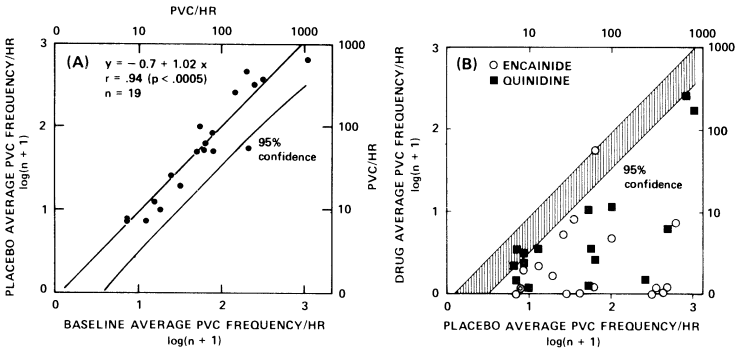


FIGURE 2. *Linear regression analysis with 95% and 99% confidence intervals of variability for baseline vs placebo measurements of average premature ventricular complex (PVC) frequency/hour of ambulatory ECG recording. Analysis was performed on the log (PVC frequency +1). The corresponding absolute values are shown on the opposing scales. The 95% and 99% confidence lines represent the one-tailed lower confidence intervals for individual data points. The sensitivity threshold is the point at which the 95% or 99% confidence line crosses the baseline of PVC frequency. Baseline frequencies below the sensitivity threshold may vary by as much as 100% between baseline and placebo recordings and cannot be used to evaluate antiarrhythmic drug efficacy.*

Figure 3.



A, linear regression analysis with determination of 95 percent confidence intervals of variability for baseline vs. placebo measurements of average premature ventricular complex (PVC) frequency/h of ambulatory electrocardiographic recording. Analysis was performed on the log (premature ventricular complex frequency + 1). The corresponding absolute values are shown on the opposing scales. The 95 percent confidence line represents the one tailed lower confidence interval for individual data points. The point at which the confidence line crosses the baseline axis determines the "sensitivity threshold" below which even total suppression of premature ventricular complexes cannot be distinguished from spontaneous variability. **B,** individual responses to encainide (**open circles**) and quinidine (**closed squares**) are plotted. The shaded area represents the 95 percent confidence intervals of variability in premature ventricular complexes. To distinguish true drug response from placebo effect at the 0.05 level of significance, the single point that describes the placebo and post-drug responses must fall below the 95 percent confidence limit. The higher the average frequency of premature complexes during placebo therapy, the lower the percent reduction required to establish drug efficacy at a given confidence level.

effective drug treatment. Dose titration in each patient until an effective plasma concentration of the appropriate drug could be used with the assumption that therapeutic effect had been achieved. This would be preferrable to any fixed dose administration program. The duration of the study should be for two years; follow-up should be monthly for the first three months, at six months, at one year, at eighteen months and twenty-four months, in my opinion, with periodic examination of the data.

ETHICAL AND MORAL CONSIDERATIONS:

Since it is not possible to carry out the proposed study with placebo comparison, a comparison of effectiveness of a Class IA and IC drug in a parallel design would seem to be the most appropriate method. Such a design would also preclude requiring that patients be free of diuretic, digitalis or beta blockade therapy. Restratification of patient groups will be possible at the conclusion of the study since in the patients selected equal distribution of the compounding variables could be assumed.

DISCUSSION:

Such a study will provide an indication of the effectiveness ot antiarrhythmic drugs in reducing sudden cardiac death as it relates to the reduction of frequent ventricular premature beats and complex forms. It will provide important information about the likelihood of reducing sudden cardiac death in these high risk stratified patient groups following myocardial infarction.

It is necessary to recognize that Class I antiarrhythmic drugs may actually increase the likelihood of sudden death by arrhythmia induction rather than decrease death and arrhythmias. In fact, this is one of the more important questions which will be answered by such a study since the arrhythmogenic action of antiarrhythmics is being reported with increasing frequency. The statistical techniques described by my colleagues and I (35, 36) will permit a determination of the quantitative reduction of arrhythmias which were thought to be independent markers for sudden cardiac death. This method will also allow for considering the spontaneous variation of the arrhythmias separate from drug effects.

Such a study is clearly fraught with many difficulties and problems as has been appreciated by Task Forces at the NIH and Veterans Administration for design of such studies. However, it seems likely that both sponsoring agencies will fund such a study during 1983-84. Therefore, the design needs careful consideration and much discussion in the cardiology community. The purpose of this presentation is to encourage interaction among the various groups necessary to perform such a study in this high risk group of patients following acute infarction.

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DO BETA BLOCKERS PREVENT SUDDEN CARDIAC DEATH?

Joel Morganroth, M.D.

The high risk patient for developing sudden cardiac death is the individual who has underlying structural heart disease and electrical instability manifesting as a ventricular arrhythmia. The event of sudden cardiac death is believed to be due to ventricular fibrillation caused by the development of ventricular tachyarrhythmia in such patients. It is the hope that after initial therapy to the underlying structural heart disease that the successful elimination of ventricular ectopy using antiarrhythmic agents can prevent sudden cardiac death.[1]

Prior to the demonstration that sudden cardiac death can be prevented by an antiarrhythmic mechanism, the definition of antiarrhythmic efficacy has relied upon statistical approaches to demonstrate that the antiarrhythmic drug has had an independen effect upon the frequency of such ectopy.[2]

Beta adrenergic blocking agents have for many years not been considered a primary means of reducing or eliminating electrical instability though in certain selected settings they have been considered the first drug of choice.[3] These include ventricular ectopy due to volatile anesthetic induced catacholamin release, ventricular ectopy due to active coronary induced ischemia, digitalis induced arrhythmias and the particular conditions of mitral valve proplase and idiopathic hypertrophic sub-aortic stenosis. Though not well-studied, the combination of beta blocking agents with typical membrane-active antiarrhythmic drugs has been believed by many investigators to be a useful antiarrhythmic combination.

Electrophysiologic effect of beta blocking agents in regard to their potential of elimimating ventricular arrhythmias has not

been clearly defined. One suggested mechanism of effect is simply the prevention of myocardial ischemia an event which can induce ventricular arrhythmias. The so-called "quinidine-like" depressant effect on the membrane which will decrease the maximum rate of diastolic depolorization of the action potential as well as delaying conduction velocity and increasing effective refractory period has been relegated to a various degree of importance. Coltart, et al[4] have provided the most convincing evidence that this so-called membrane stabilizing effect is not clinically important. In addition, various types of beta blocking agents with different degrees of so-called membrane stabilizing effect seem to be identical in terms of their antiarrhythmic efficacy (Table 1) arguing against the importance of the membrane stabilizing effect of the beta blockers as an important cause of their antiarrhythmic action.

TABLE 1

Pharmacologic Factors of
Beta Blockers in Relation to
Ventricular Arrhythmia Reduction

	CS	ISA	Membrane Effect	% VPC Reduction*
Propranolol	-	-	+	about 50%
Metoprolol	+	-	-	"
Nadolol	-	-	-	"
Atenolol	+	-	-	"
Acebutolol	+	+	+	"

* In chronic arrhythmia studies
VPC=ventricular premature complexes
CS=cardioselectivity
ISA=iatrinsic sympathominmetic activity

The most important mechanism of beta blocking effect as an antiarrhythmic is probably in inhibition of the adrenergic stimulation effect. Beta blockers do reduce the slope of Phase IV diastolic deplorization of pacemaker cells to counteract the adrenergic effect on increasing the rate of diastolic deplorization in rate of impulse.

Table 2 demonstrates the conditions in which beta blockers have been shown to be clinically useful in eleminating ventricular arrhythmias.[5-11] Of particular note is that they appear to be successful in patients with high risk of sudden cardiac death, i.e., in those patients with underlying structural heart disease as well as ventricular arrhythmia.

TABLE 2

USE OF BETA BLOCKERS IN VARIOUS CLINICAL STATES

	Condition	BB	% Responding
Nixon	Exercise-induced VPCs	Propranolol	66%
Aronow	Digtoxic VPCs	Pindolol	71%
Winkle	Mitral Valve Prolapse	Propranolol	56%
Woosley	Mixed Cardiac States	Propranolol	75%
Pratt	Mixed Cardiac States	Metoprolol	54%
Koppes	Acute Myocardial Infarct.	Propranolol	56%
Podrid	Mixed Cardiac State	Pindolol	50%

In 1981-1982, large cooperative clinical trials using beta blockers in patients post-myocardial infarction have all demonstrated a decreased rate of sudden cardiac death in patients treated with beta blockers compared to the parallel placebo control group.[12]

The effect of beta blockers on the electrical instability in these patients has not been clearly defined as yet but prelminary

information is important to review. In the cooperative metoprolol trial performed in Sweden concerning the effect of metoprolol compared to placebo in post-infarction patients, episodes of ventricular fibrillation were encountered.[13] The placebo group had 17 episodes of ventricular fibrillation in 697 patients compared to only six episodes of ventricular fibrillation in 698 treated with metoprolol. This difference was just statistically significant.

Preliminary data on the effect of sotalol in a similar trial conducted in the United Kingdom is available in 107 patients.[13] Patients on sotalol had fewer episodes of ventricular complex arrhythmias (ventricular couplets and ventricular tachycardia) and it appears that sotalol prevented the increased rate of rise in the frequency of ventricular ectopy from baseline to one month post-myocardial infarction.

Preliminary data are also available from the Beta Blocker Heart Attack Trial conducted in the United States.[14] In that study, 1921 patients received placebo and 1916 patients received propranolol in a multi-center cooperative controlled study conducted by the National Institutes of Health. All patients had a documented myocardial infarction and prior to receiving either placebo or propranolol all patients had a 24-hour ambulatory Holter monitoring performed which was analyzed in a central laboratory using sophisticated soft-ware computerized technology. Excellent internal and external quality control methodology were employed. After institution of either propranolol or placebo, 953 patients, approximately one-quarter of the group, had a second 24-hour monitoring session performed at approximately six weeks post-myocardial infarction. As of this writing, approximately 650 patients who had both a baseline and repeat Holter monitor at six weeks have been fully analyzed and are herein reported. The 655 represent approximately 70% of the 953 patients who had this second six-week ECG recording of their arrhythmia profile.

Table 3 details the ventricular arrhythmia frequency at baseline using several categories of types of ventricular

arrhythmias and demonstates that there was no statistically significant difference among these types of arrhythmias prior to randomization in patients who received propranolol compared to those who received placebo.

TABLE 3

PERCENT WITH TYPES OF
VENTRICULAR ARRHYTHMIAS AT BASELINE N=655

	Propranolol	Placebo
No VPCs	16.7	13.9
VPC $\geq$ 10*	13.3	16.3
VPC $\geq$ 30	6.5	7.9
Any VC/VT	24.2	21.8
VPC $\geq$ 10 + VC/VT	8	9
VPC $\geq$ 30 + VC/VT	5.2	5.7

* mean per hour per 24 hours

VPC= ventricular complexes
VC = ventricular couplets
VT = ventricular tachycardia

In addition, the baseline clinical characteristics of patients who received propranolol or placebo are demonstrated in Table 4 and show no statistical differences in the type of underlying structural or metabolic abnormalities between the two groups.

TABLE 4

BASELINE CLINICAL CHARACTERISTICS N=655

	Propranolol (%)	Placebo (%)
Mean	83.6	85.5
Previous M.I.	16.7	13.9
Anterior M.I.	30.4	24.5
Inferior M.I.	31.0	31.6
CK Ratio 2-8x	43.5	44.8
CK Ratio 8-15x	32.7	28.3
CHF + Digoxin Use	4.8	4.1
Digoxin Use	6.0	4.1

MI = Myocardial Infarction
CK = Creatine Kinase
CHF= Congestive Heart Failure

The results of the natural history evaluation of the effect of propranolol versus placebo on the frequency of ventricular arrhythmias are demonstrated in Tables 5 and 6. We have chosen the criteria of daily mean ventricular ectopy (VPC) $\geq$ 10/hr. and a second criteria of VPC $\geq$ 10/hr plus complex ventricular arrhythmias (defined as ventricular couplets and/or ventricular tachycardia) for analysis. These cut points were chosen using the epidemiological information provided by Bigger et al[14] in which the population with these arrhythmia criteria appears to be in particular at high risk of sudden cardiac death post-myocardial infarction. The data in Tables 5 and 6 demonstrate quite clearly that there is a marked increase in the prevalence of simple and complex ventricular arrhythmias from baseline compared to six weeks in patients on placebo (a doubling to tripling of the frequency of simple and complex events respectively) but that this increase is markedly blunted (less than a 2x increase) in patients on propranolol. Using paired patient data (Table 6) it is quite clear that the absence of ventricular ectopy at baseline does not insure that ventricular ectopy will not be

present at six weeks. In fact over a fifth (24%) of the population on placebo developed simple and complex ventricular arrhythmias at six weeks when absent at baseline, whereas patients on propranolol had an approximate one-half of this increased prevalence (12%). In those patients with ventricular arrhythmias at baseline far more continued to have these arrhythmias while on placebo at six weeks (69%) than in the propranolol group (56%).

TABLE 5

NATURAL HISTORY OF VENTRICULAR ARRHYTHMIAS
FREQUENCY FROM BASELINE TO SIX WEEKS
AFTER MYOCARDIAL INFARCTION

	Propranolol		Placebo	
	VPC ≥ 10*	VPC ≥ 10+VC/VT	VPC≥10	VPC ≥10+VC/VT
At Baseline (N=655)	13%	8%	16%	9.1%
At Six Weeks (N=654)	21%	15%	35%	27%

* mean per hour per 24 hrs.

TABLE 6

NATURAL HISTORY OF VENTRICULAR ARRHYTHMIAS
IN THE PROPRANOLOL GROUP COMPARED TO
PLACEBO FROM BASELINE TO SIX WEEKS AFTER
MYOCARDIAL INFARCTION

		VPC≥10/hr at Six Weeks			
		Propranolol (%)		Placebo (%)	
VPC ≥ 10/hr* at Baseline	(yes)	48.8	(20/41)	71.7	(38/53)
	(no)	17.5	(48/285)	28.3	(75/265)
VPC ≥ 10+VC/VT at Baseline		*VPC≥10/hr+VC/VT at Six Weeks*			
	(yes)	56	(14/25)	69	(20/29)
	(no)	12	(35/91)	23.5	(68/289)

* mean per hr. per 24 hrs.

In conclusion, this preliminary information clearly identifies that beta blockers do have an important effect on ventricular ectopic instability in patients post-myocardial infarction. With the clear decrease in sudden cardiac death reported in the recent cooperative beta blocker clinical trials, it is reasonable to hypothesize that the antiarrhythmic properties of these beta blocker drugs are important in the prevention of sudden cardiac death. Preliminary data from the BHAT data as presented in Tables 5 and 6 and other data yet to be reported suggest that the sudden death mortality in patients with less ventricular ectopy in the propranolol group compared to the placebo group is decreased which would tend to support this hypothesis. Since none of the large scale beta blocker trials were conducted with the primary purpose of demonstrating the antiarrhythmic effect of beta blockers and that role in the prevention of sudden cardiac death, new trials specifically designed to test this hypothesis will be necessary before one can definitively answer this question.

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DOES NON BETA-BLOCKING ANTIARRHYTHMIC THERAPY PREVENT SUDDEN CARDIAC DEATH?

R.W.F. CAMPBELL

INTRODUCTION

Prevention of sudden cardiac death is an important medical goal. Improved understanding of the natural history of a variety of cardiac conditions has increased the accuracy with which high risk patients can be identified and has emphasised the need for effective and non-toxic interventions. That ventricular fibrillation is probably the most common cause of death is supported by observations from out-of-hospital rescue squads and from continuous electrocardiographic tape recordings.

Prophylactic administration of beta-adrenoreceptor blocking agents to survivors of acute myocardial infarction can improve their prognosis(1) and it is likely that in subsequent years the specificity and power of this secondary prevention will be improved. By contrast, non-betablocking antiarrhythmic drugs which might be anticipated to prevent ventricular fibrillation have, as yet, not been shown to be effective despite the ability of these agents to benefit individual patients. What are the reasons for this apparent paradox? Poor study design, inappropriate patient selection, inadequate dosing and ineffective

drugs are some possible explanations. Importantly, in almost all such studies either the number of patients investigated has been too few or the incidence of ventricular fibrillation has been too low to permit a meaningful statistical assessment of administered therapy.

EVIDENCE THAT NON-BETABLOCKING ANTIARRHYTHMIC DRUGS CAN CONTROL LIFE THREATENING VENTRICULAR ARRHYTHMIAS

Placebo controlled studies of antiarrhythmic drug treatment of life threatening ventricular arrhythmias are ethically unacceptable. Most available evidence for drug action in this clinical context is inferred from drug effects against non-life threatening ventricular arrhythmias and by extrapolation from drug use in individual patient management. Conclusions based on such data may prove misleading when appraising the applicability of a drug for the prophylaxis of ventricular fibrillation.

Assessment of Antiarrhythmic Drug Action

Antiarrhythmic drug licencing depends upon the demonstration of efficacy and safety. The classical clinical model is the patient with chronic stable cardiac arrhythmias who may not require treatment, but in whom thorough scientific evaluation of drug effect is possible with minimal risk. Comparison of drugs to prove antiarrhythmic superiority, reduced toxicity or to demonstrate a broader spectrum of action becomes possible in this clinical context.

In the past, extrapolation of a useful drug effect on chronic stable arrhythmias particularly frequent ventricular ectopic complexes, to an action on ventricular fibrillation has seemed logical, but such assumptions are now known to be erroneous. In acute myocardial infarction, ventricular tachycardia and ventricular fibrillation have different time correlations, arrhythmia associations and fundamental mechanisms(2). By contrast with ventricular fibrillation, ventricular tachycardia frequently is self-terminating. Single ventricular ectopic complexes and ventricular tachycardia and R-on-T ventricular ectopic complexes and primary ventricular fibrillation may be more directly related to each other but even this association is observed in analyses of highly selected patient groups in the acute phase of myocardial infarction and the relationships may be different in the late phase of infarction, in myocardial ischaemia and in cardiomyopathic states.

Individual Clinical Experience

Drug selection for treatment of individual patients is usually empirical but modified by physician preference and by the known clinical characteristics of the patient. For example, procainamide might be preferred to disopyramide in the management of a patient with ventricular tachycardia and a history of prostatism. By trial and error an effective and well tolerated regime often can be found but it will be highly individual for that patient and his arrhythmia.

All practising cardiologists can attest to the performance of one or more antiarrhythmic drugs by the evidence of their

personal experience of arrhythmia management. Such a clinical assessment requires knowledge of the expected natural history of the patient's problem as no simultaneous comparative control observations are available.

Individual case experiences whether of drug success or failure, are unlikely to be published. Based on personal experience, drug assessment would be severely biased by the availability and priority of use of individual agents. For example, in the United States quinidine and procainamide might be tested at an early stage for the management of a life threatening ventricular tachyarrhythmia whilst in the United Kingdom, mexiletine and amiodarone probably would feature more prominently. However, consistent and complete registration of drug use in large populations may be the only way to establish the relative efficacy of antiarrhythmic therapy in the management of arrhythmias which are too dangerous to investigate in controlled studies. In the United Kingdom, the licensing of amiodarone by the Committee on Safety of Medicines was justified by the accumulated evidence of its important efficacy against life threatening ventricular arrhythmias which had proved resistant to currently available preparations. Data from a register of the emergency use of tocainide has been reported(3) and suggests an important role for this agent when compounds currently available in the United States, have proved ineffective.

NON-BETABLOCKING ANTIARRHYTHMIC AGENTS IN POPULATION STUDIES

Myocardial infarction has a high initial mortality probably from ventricular fibrillation. Survivors of this acute phase have a variable subsequent prognosis but a moderately accurate assessment of risk can be derived from readily available clinical evidence. The possibility of mortality reduction by non-betablocking antiarrhythmic therapy in both the acute and post-hospital phase of infarction, has been assessed in a number of investigations.

Prophylaxis of ventricular fibrillation in acute myocardial infarction.

Ventricular fibrillation in the early hours of myocardial infarction reflects acute electrical instability rather than extensive irrecoverable cardiac damage. Follow-up of successfully defibrillated survivors of primary ventricular fibrillation (ventricular fibrillation in the absence of shock or cardiac failure) reveals their prognosis to be little different from that of patients whose infarction was not so complicated(4,5,6). However, whilst prompt and effective defibrillation can achieve these excellent results, a successful drug regime for the prophylaxis of primary ventricular fibrillation would have an important application in situations where defibrillators were not available and use could be restricted to high risk patients identified simply as those within the first 6 or 12 hours from the onset of symptoms. In only one of many investigations has a significant reduction of primary ventricular fibrillation been acheived. However,

mortality in this high dose intravenous lidocaine study(7) was uninfluenced, defibrillators being available to resuscitate those who developed ventricular fibrillation. The result suggested that if the lidocaine regime were used out-of-hospital where defibrillators were not readily available, the acute phase mortality of myocardial infarction could be reduced through prevention of primary ventricular fibrillation. Unfortunately, the need to give lidocaine by the intravenous route necessitates trained personnel and they might just as appropriately defibrillate the small number of patients who develop this complication. An out-of-hospital use of intravenous lidocaine has been reported and whilst there was a significant reduction in mortality, this investigation was seriously flawed by an anomaly of patient randomisation(8). No confirmatory study has been conducted. Intramuscular lidocaine appears not to be effective in preventing primary ventricular fibrillation(9) and other reports of lidocaine use are predominantly uncontrolled observations. Oral regimes for the prophylaxis of ventricular fibrillation have been investigated with procainamide(10), quinidine(11), mexiletine(12), tocainide(13), but a beneficial reduction of primary ventricular fibrillation has not been demonstrated. Most of these studies had little chance of detecting a useful drug effect even if it existed as the study populations were small and the incidence of primary ventricular fibrillation was low.

It is reasonable to conclude that high dose intravenous lidocaine can prevent primary ventricular fibrillation and can therefore reduce mortality in acute myocardial infarction if used when resuscitation facilities are unavailable. Whether, in other situations, the widespread utilisation of prophylactic lidocaine regimes is indicated, remains a matter of controversy(14,15).

Prophylaxis of Sudden Death Following Myocardial Infarction.

The post hospital course of acute myocardial infarction is variable. Patients with minor myocardial damage and no complications have a low mortality in the first year. By contrast patients with substantial myocardial damage have an important subsequent risk of death. Current evidence suggests that while some will succumb because of their extensive infarction, death is frequently a consequence of ventricular fibrillation. Immunerable secondary prevention studies have been conducted and apart from those recently reported with beta-adrenoreceptor blocking drugs(16,17,18), mortality has been uninfluenced. The many possible explanations for this relate to study design, included patients, and the antiarrhythmic drugs selected.

Study Design. The positive beta-adrenoreceptor blocking studies(16,17,18) randomised 1395 to 3837 patients with a 27% to 38% mortality reduction over the follow-up period. No secondary prevention study using non-beta-blocking drugs has been of such size and a positive effect of therapy might have been obscured within the small

populations enrolled (Type II error).

Patients Selected. In general, relatively low risk populations have been recruited to secondary prevention studies of both beta-adrenoreceptor blocking and non-beta-adrenoreceptor blocking drugs. In two studies, one of mexiletine(19) and one of aprindine(20), high risk patients were deliberately identified and despite small numbers, drug modification of their natural high mortality might have been expected to be identified but occurred in neither. However, these patient groups contain individuals at high risk of cardiac death from non-arrhythmic mechanisms for example, further infarction, rupture and failure and it is possible that any antiarrhythmic benefit was counter-balanced by the natural or aggravated mortality from mechanical death.

Antiarrhythmic Drug Factors Drugs selected for secondary prevention trials usually have proven efficacy against stable ventricular arrhythmias yet this effect maybe meaningless for ventricular fibrillation prophylaxis. In experimental situations, drugs which prolong refractoriness (the Vaughan Williams Class III antiarrhythmic action(21)) are the most effective antifibrillatory agents. However, amiodarone the most important clinically available drug of this class has not been tested for ventricular fibrillation prophylaxis in large populations largely because of its not inconsiderable toxicity(22). When newer, less toxic agents, possessing class III actions become available, they may prove successful in secondary prevention following acute myocardial infarction.

The dosing regime employed in secondary prevention studies may be of critical importance. Most investigations use a fixed dose or a dose dependent upon the patient's weight. Individual dosing whilst ideal, is complicated and expensive if double blind study conditions are to be maintained. Individual management implies drug dosing variations to achieve a clinical objective, for example, a certain plasma drug level or a 95% reduction of ventricular ectopic complex rates. When the aim of theray is to prevent ventricular fibrillation, interactive dose variations based on this end point are impossible. Dosing dependent upon plasma drug levels is possible though tedious but has the attaction of identifying non-compliers and of providing substantial population data on drug pharmacology. Recent reports of sudden death prophylaxis in survivors of out-of-hospital ventricular fibrillation, suggest that individual dosing to the maximum tolerated without serious unwanted effects is an effective clinical strategy(23).

Prevention of Sudden Cardiac Death in other Cardiac Conditions.

Sudden cardiac death is associated with a variety of cardiac conditions including aortic stenosis, cardiomyopathies, the pre-excitation syndromes, mitral valve prolapse and the congenital long QT syndromes. Arrhythmic death is associated to a varying degree with all but the need, use and selection of antiarrhythmic therapy is individually decided and would not necessarily include non-beta-blocking antiarrhythmic drugs. Indeed, non-beta-blocking agents appear of little value for the prophylaxis of sudden death in the long QT syndromes whilst

beta-adrenoreceptor drugs are the medical treatment of choice(24).

FUTURE STUDY DESIGNS FOR SECONDARY PREVENTION OF SUDDEN CARDIAC DEATH AFTER MYOCARDIAL INFARCTION.

Secondary prevention drug studies, in addition to testing drug action, must be clinically relevant. Fixed dose single drug treatment is quite different from clinical practice where individualised therapy is offered. The European Society of Cardiology's Working Group on Arrhythmias and Electrophysiology is currently discussing a new proposal, the Lubsen ESC protocol, which aims to test non beta-adrenoreceptor blocking drug effectiveness post-myocardial infarction in selected high risk patients (defined by their having continued non-life threatening ventricular arrhythmias in the late hospital phase of acute infarction). An antiarrhythmic drug will be given and "responders" and non-responders" identified. "Non-responders" will receive other agents until only a few true "non-responders" remain. "Responders" to each agent will then be randomised to receive that active drug or placebo and their subsequent progress will be monitored. There is ethical justification for this approach as there is no proven benefit of administering antiarrhythmic therapy for non-life threatening ventricular arrhythmias after acute myocardial infarction. The use of beta-blocking drugs or other drugs is not precluded by this study design.

The role of non-betablocking antiarrhythmic drugs in the prevention of sudden cardiac death can be answered only by new, large, well designed and clinically relevant studies. A valid and useful conclusion will result only if such investigations are flexible enough to incorporate new advances in cardiological practice.

INTERVENTIONS OTHER THAN ANTIARRHYTHMIC NON-BETABLOCKING DRUGS

Sudden cardiac death can be modified by drugs other than antiarrhythmic agents(25). Drugs which prevent ischaemia, which alter thrombotic factors and which reduce infarct size in the event of infarction could all exert a useful immediate or late benefit. As yet, none has been identified so certainly as to be recommended for clinical practice. Non-drug interventions also have an important role for the reduction of sudden cardiac death(25). The relevance of surgery, pacing and implanted defibrillators to this present discussion lies with their interaction wih drug management of sudden death. Almost all survivors of acute myoardial infarction have intrinsic coronary artery disease and for some, surgical rather than medical prophylaxis of sudden death may be more appropriate. Prevention of sudden cardiac death can be effected by a variety of interventions and an urgent priority must be to identify which is optimal for any particular clinical situation.

CONCLUSIONS

Sudden cardiac death occurring in asymptomatic, apparently

normal individuals is a tragedy about which little can be done until acceptable diagnostic methods are developed to identify latent disease. Sudden cardiac death in patients who identify themselves by an acute myocardial infarction or other cardiovascular pathology is more amenable to prophylaxis. Yet proven preventative measures are few. The identification of the value of prophylactic beta-adrenoreceptor blocking drugs following myocardial infarction is an important advance. The studies in which these drugs were investigated were designed to acheive a statistical conclusion, required large populations, employed many centers and were expensive to conduct. Non-beta-adrenoreceptor blocking antiarrhythmic drugs usually have been examined in small populations by individual institutions. Very few large scale studies of these drugs have been conducted and probably none as yet reported, has been of a size where a positive benefit might have been statistically confirmed. The design of non beta-blocking antiarrhythmic drug studies is complicated by the enormous variety of actions of individual agents. Beta-adrenorector blocking drugs, by contrast, probably all operate to reduce mortality by the same mechanism. Non-beta-adrenoreceptor blocking drugs selected for investigation may have had inapproprate electrophysiological actions to prevent ventricular fibrillation or alternatively may have been used in study designs where blood levels were unacceptable either through inappropriate dosing or when adverse effects have encouraged non-compliance.

There remains considerable scope for further measures to prevent sudden cardiac death. Beta-adrenoreceptor blocking drug use probably achieves mortality reduction of around 20% leaving a continuing mortality which is uninfluenced by the action of these agents. Controversy exists as to the proportion of at risk patients with myocardial infarction who can safely take beta-adrenoreceptor blocking drugs without jeapordising left ventricular function. There are thus many reasons for further trials of non-betablocking antiarrhythmic drugs using good study designs and appropriately selected patients and drugs. Protocols need to incorporate the expanding knowledge of the natural history of populations, of the actions of drugs and of the response of individuals to drugs. Scientific research of drug effectiveness should closely match clinical practice and should permit the use of other interventions when appropriate without invalidating the investigation.

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CURRENT PROBLEMS IN THE EVALUATION AND APPROVAL OF NEW ANTIARRHYTHMIC AGENTS

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It seems a very short while ago that many of the people here today convened to consider "The Evaluation of New Antiarrhythmic Drugs". Many of the issues that concerned us then are still pertinent, including how to define effectiveness, the role of acute electrophysiologic testing, and (the ultimate question) whether there was some good way to evaluate the effectiveness of drugs in reducing mortality. Some of the most difficult problems may even have become more complicated by the appearance of a "superstar" agent, antiarrhythmic heavens, amiodarone, which many believe violates what were on their way to becoming accepted rules about how to choose therapy.

From the viewpoint of a regulatory agency, evaluation of antiarrhythmic agents has features that make our decisions both extremely easy and very difficult: they are easy because the evidence of relevant pharmacologic activity, i.e. suppression of some arrhythmias, is almost trivially simple to obtain, yet difficult because what we most want to know seems to be almost impossible to study rigorously. With modern Holter analysis techniques, it is a straightforward matter to define the effect of a drug on any reasonably common arrhythmia and, for a given patient, the effect on total VPB's, couplets, and runs of various lengths, can be readily quantitated. Not only that, some members of the current crop of antiarrhythmics have such profound effects on these abnormalities that concurrent control groups are scarcely necessary; their effects are self-evident. Historically, FDA has accepted well-controlled studies showing an ability to reduce the frequency of these events as evidence of effectiveness, and no major change in this position is anticipated, so far as evidence of effectiveness is concerned.

Effects on arrhythmia frequency, however, while important, are not what we most want to know about, which brings us to the first problem.

1. What we can and do measure is not necessarily what we really want to measure.

Although in some cases arrhythmias are treated to provide symptomatic benefits, the largest portion of drug therapy is for asymptomatic arrhythmias and the purpose of treating them is to prevent hemodynamically unstable, potentially fatal arrhythmias. As Winkle said years ago, "drug trials showing efficacy for asymptomatic ventricular arrhythmia suppression are only a preliminary to, and not a substitute for, demonstrating a drug's capacity to prevent recurrent symptomatic ventricular tachycardia or sudden death"[1]. Yet concurrently controlled trials of antiarrhythmic agents that are intended to assess effects on mortality have been rare and, when carried out, have on the whole not shown benefit. There are a number of possible reasons for this, including:

a. The best drugs may not have been tried,
b. The highest risk populations (most likely to show a benefit) do not enter this kind of trial, at least not often,
c. The conventional drug trial (one drug vs. placebo or one drug vs. a control drug) is the wrong trial because it leads to inadequate drug selection procedures.

It is possible, of course, that some of the newer drugs that seem able to suppress nearly 100% of VPB's would be successful in mortality trials even in a straightforward one drug vs. placebo comparison in patients whose only abnormality is frequent VPBs. It may be particularly important to choose the right population and pay close attention to associated risk factors. Califf, et al have recently reported[2], as others have, that prognosis in patients with arrhythmias on ambulatory monitoring is critically dependent on the presence of coronary artery disease and on abnormalities of left ventricular function. A high risk population with these features would seem to offer the best opportunity to show improvement in survival, so long as treatment groups are well-matched.

Even with the newer agents, however, there is still reason to wonder whether a conventionally designed trial is the right kind. All antiarrhythmic agents sometimes make arrhythmias worse[3], and may be the cause of life-threatening arrhythmias[4]; this may be more likely

in patients with poor prognosis. It may be necessary to select drug therapy in some way in order to alter prognosis.

In patients with documented, hemodynamically unstable arrhythmias, presumably the group in which antiarrhythmics would be most likely to have a favorable effect on mortality, conventional controlled trials are rarely even considered. Instead, we see open, "historically controlled" studies, many of which are extremely hard to evaluate because populations and interventions are often not well-defined. In these patients, however, drug therapy is usually selected in some way, either by Holter monitoring, effects on exercise induced arrhythmias, or effects on electrically induced arrhythmias.

Perhaps the purest kind of historically controlled study is typified by Ruskin's[4] and others' studies in patients surviving non-infarction related cardiac arrest, in which results of electrophysiologically-selected drug therapy can be compared with historical experience in a comparable (one hopes) population and with a kind of internal control group. The internal control in these studies, which not a randomly assigned control, is the group of patients in whom no regimen can be found that suppresses their programmed stimulation-induced arrhythmia. Most studies of this kind have shown that the group with suppression of induced arrhythmia carries a highly favorable prognosis, compared to the group that cannot be suppressed. There remains, of course, the nagging possibility that the poor prognosis in the non-suppressible reflects their disease state, i.e., an inherently worse prognosis, not their response to treatment.

The results of these kinds of trials have been impressive enough to cause us to conclude that a modern evaluation of an antiarrhythmic agent should include assessment of its ability to suppress programmed stimulation-induced arrhythmias. Of course, suppression of induction is not the real purpose of therapy any more than VPB suppression is, but it seems at least as pertinent to ultimate effectiveness as an ability to reduce the VPB rate. So far, all drugs active against VPB's have been able to block induced arrhythmias, at least in some patients. No one has, to my knowledge, in a systematic way tried to compare agents for their ability to suppress induced arrhythmias, e.g., by randomizing the sequence in which the drugs are tried in newly identified patients with

arrhythmias. Generally, the newer agents have been tried only in patients who have failed on the older ones, such as quinidine and procainamide. Presumably, such patients are relatively resistant to suppression, and the newer agents do not seem very different from the older ones in their ability to suppress. It may be, however, that some drugs will prove more consistently effective in suppressing stimulated arrhythmias than others, when this is properly studied.

The studies of stimulation suppression certainly suggest a relation of suppression to survival in patients with documented life threatening arrhythmias, but they are not rigorously controlled trials of effects on survival and they have not usually compared suppression of stimulation with other, non-invasive, modes of drug selection. It may also prove difficult to apply this impression that drug selection by programmed stimulation is effective in very high risk patients to other cases. We do not know for example, whether it is feasible to carry out a trial in high-risk post-infarction patients without known hemodynamically unstable arrhythmias if the trial involved so invasive a procedure as programmed stimulation. We also do not know what fraction of such patients would prove to be stimulatable. Despite these difficulties, it is crucial to consider how drug therapy in mortality trials is to be selected. Even considering this, however, raises a second major problem.

2. Although mortality effects of antiarrhythmics probably relate more to the technique of drug selection than to the specific drug selected, clinical investigation resources tend to be focussed on single drugs.

The focus of drug development has, reasonably enough, been specific drugs, each developed by a particular drug company. For treatment of serious ventricular arrhythmias, however, it is now apparent that a physician cannot plan to use a single agent nor even select therapy on the basis of a clinical picture. He must, in most cases, resort to trial and error, perhaps choosing the agents he is most familiar with first or choosing those first that are best tolerated. In carrying out the trial and error procedure, the end points are determined in part by the clinical presentation, and in part by physician choice. Where the arrhythmia is frequent, its suppression can be detected by ECG or Holter monitoring. Where it is not, or where a more serious problem than the

easily observed arrhythmia is suspected, some provocative test, exercise or electrical stimulation, must be used. In fact, given the ability of most agents to make at least some patients susceptible to serious arrhythmias where they were not before, it might be argued that provocative testing is more important than generally recognized and should accompany most use of antiarrhythmics, even if most patients are not inducible prior to drug therapy.

In any case, it appears that no single drug will prove regularly effective in suppressing serious arrhythmias, however therapy is chosen. It follows that a trial to discover the effect of treatment on serious arrhythmias must be more a trial of drug selection techniques than a trial of the individual drugs themselves. This is not the sort of trial drug companies can easily carry out; such trials therefore await a mechanism that can examine many agents at the same time. The need for such a trial is very great because at present drugs are assigned to patients without known unstable arrhythmias on the basis of Holter monitoring or even less (rhythm strips) and we have reason to think this is not adequate. Zipes' group, in the American Journal of Cardiology[5], recently reported that in patients with ventricular tachycardia and no coronary artery disease, a favorable response to therapy, as assessed by programmed stimulation, was uniformly associated with non-recurrence of arrhythmia during long-term treatment. On the other hand, a favorable response, as assessed by non-invasive testing, did not correlate with a good subsequent clinical course. Similar favorable results of programmed stimulation have been reported in patients with coronary artery disease and arrhythmias.

On the other hand, in the June 1982 American Heart Journal, Graboys[6] cites some of the many questions that still need to be answered about electrophysiologic testing, which are especially pertinent to the patient without a documented life-threatening arrhythmia, but who has a high VPB rate and a poor prognosis:

1. How essential is electrophysiologic testing in patients with life-threatening arrhythmias? Can an adequate regimen be chosen by ECG monitoring and exercise stress testing?

2. How often do asymptomatic patients respond to stimulation with development of VT and what does it means if they do? Do they need antiarrhythmic therapy?
3. What stimulation regimens and endpoints are most predictive of outcome and are least dangerous to the patient?
4. How do results reported to date from tertiary care centers relate to the far larger populations seen and treated by local practitioners?

A mechanism for studying many drugs at once would make it possible to consider such questions and examine therapeutic interventions in a variety of clinical pictures, including both the very high risk patient (post-resuscitation, hemodynamically unstable VT, etc.) and lower risk patients. Up to now, treatment of high-risk post-infarction patients without apparent serious arrhythmias has seemed best evaluated by a randomized trial of drug vs. placebo, but here too, therapy choice could be critical, as there is little doubt drugs will place some of them at increased risk. Such a trial therefore needs some method to choose therapy, whether it is Holter monitoring, exercise or programmed electrical stimulation, and the methods need to be compared.

There had, I think, been growing recognition of the need to select therapy in some consistent way until the advent of a possibly different sort of drug distracted the process. In the view of some, amiodarone is a drug that does not follow the rules, a drug that works very well whether or not it suppresses inducible arrhythmias and that is very likely to work in any given patient.

Unfortunately, the problems of evaluating antiarrhythmic therapy in uncontrolled settings are at their worst for amiodarone, whose effects are commonly seen after a long time, leaving ample opportunity for the patient's status to change. Moreover, reports from excellent investigators vary considerably, some reporting that supression of induced arrhythmias is largely irrelevant, others finding much better results when suppression is attained.[7]

Amiodarone may be most important because of its effect on thinking about drug selection. As a therapeutic choice, at least if the currently used doses prove needed, it will probably always be limited in its use, because it displays a remarkable array of exotic adverse effects. It has

raised the possibility, however, of a drug "for all seasons," one that could be used most of the time, avoiding the difficult process of selection.

Up to now, the difficulties of carrying out well-controlled comparisons of drug selection techniques, or trials in which such techniques are used to choose a drug, which then would be compared to placebo, have kept such trials from being carried out. In fact, few controlled trials with mortality end points of any kind have been carried out. Instead, apart from controlled studies of stable arrhythmias we have a vast, largely unplanned, virtually unanalyzable mass of open-label treatment experience with a good dozen drugs, usually in patients "unresponsive" to other therapy. It is remarkable how often responses are deemed "favorable" in these settings, and how inprecise that designation seems to be. This may reflect a third problem.

3. Nomenclature for describing crucial aspects of arrhythmia status (type, frequency, severity) is highly individual and unsystematic, especially with respect to describing therapy response.

In open studies of antiarrhythmics in seriously ill patients, the description of baseline condition and response to prior therapy does not use a common language, or perhaps the language looks different because the protocols used are so different.

You often cannot tell, for example, what previous therapy was tried, nor what dose was used, nor what constituted "failure" of prior therapy. It is sometimes not clear whether the failure drugs were administered by the current investigator during the present admission or by someone else at another time. Compliance with earlier treatment is not characterized and even dose may not be known. Even if the same investigator tried the previous drug, reports are usually skimpy as to exactly why the therapy was considered a failure; i.e. exactly what happened (type, frequency of arrhythmia).

Some organized, consistent protocol and set of descriptions would make even these uncontrolled data potentially useful in drug evaluation. At present open studies provide some useful information on safety, especially non-cardiovascular safety, and little more.

There is, I think, an easily stated, but hard to accomplish, way to solve these problems: some centralized organization that can focus on problems of therapy, not specific drugs. One tends to think of federal agencies in this context and, in fact, NIH is considering elements of such a role. But there are other possibilities and the rewards to many parties are potentially so significant that possible commercial support should not be discounted.

Obviously, as the previous speakers at this symposium have shown, individual investigators can raise hypotheses and develop techniques to be tested, and their efforts are essential to design of the large scale trials that can answer the essential questions, namely: What are the effects of treatment on survival in various groups of patients and how does method of selection of treatment affect the result, if it does? Within a method of selection, do some drugs prove more successful than others, perhaps for unsuspected reasons, such as compliance, pharmacokinetic factors, or drug-drug interactions? Individuals can shape these studies but they cannot answer the questions.

It may be, however, that the numbers of patients needed to answer such questions are not so large as might be supposed. Post-infarction beta-blocker trials have detected 25-45% reductions in mortality in populations with an annual mortality of 10-15% using study groups of 1000-1500 patients. If mortality is higher (e.g., the 20-30% mortality Dr. Bigger described for some subsets of his population) and drug effect longer, the study populations needed could be quite small. Although a single hospital could hardly carry out such trials in a reasonable time, it is not difficult to imagine a consortium of hospitals in, e.g., Philadelphia, New York, and Boston, with a cachement population of 10-15,000,000, that could carry them out readily. But this would take a level of organization, and perhaps suppression of individuality, now unheard of. The answers that could emerge would, I think, be well worth it, both to the public and perhaps to a group of commercial sponsors willing to provide support. The enthusiastic use of antihypertensive agents that has followed evidence that therapy prolonged life should indicate the potential here. Depending on the results, documentation of a real benefit from antiarrhythmic therapy in asymptomatic people would be expected to provoke a similar response. This will not happen, at

least I hope it won't, until the benefits of specific treatment regimens are documented. Enthusiastic treatment of such patients before a demonstrated life-prolonging benefit is shown has a substantial potential for doing no good or causing harm.

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Dr. Morganroth: Was there a difference in the method of analysis in the mexiletine study in terms of how the Holter monitoring data versus the mortality data. Was the intention to treat methodology used for both or only used for the mortality, maybe that explained the difference in response rate. Wasn't it also true in the aprindine study that the subgroup in which ventricular ectopy was suppressed at a high level. The mortality was statistically significantly less in the treated group than in the placebo group. That is, if one looks at analysis techniques and some parts of the population that in fact one may find that mortality can be decreased with antiarrhythmic therapy in that population.

Dr. Campbell: The mexiletine analysis was by intention to treat, so in fact the arrhythmias and the mortality were analyzed on the same basis and although a very useful effect on arrhythmias was seen, it appeared merely a cosmetic effect in the electrocardiograms but there was no benefit seen to the patients in terms of mortality reduction. The study was a small one, but it was in patients selected on the basis of their being at high risk. The basis of that high risk was on complications of the infarction in the early stage of the event and included cardiac failure, persistent sinus tachycardia and ST segment elevation. With regard to the aprindine study, it is certainly true that in the phenytoin studies and the aprindine studies, there have been minor points which have suggested that subgroups of patients have shown a statistically significant reduction in mortality if the drug were effective in these patients as determined at high plasma levels of phenytoin or impressive arrhythmia reduction in the aprindine study. It is on the basis of these hints that we are interested in this other protocol to see whether patients who respond to these drugs in an antiarrhythmic sense will respond with

mortality reduction.

Dr. Rapaport: In the analysis of these studies the aprindine, the Ghent--Rotterdam study was the only one that actually took the high risk subgroup of complex ectopy and randomized at that point in contrast to the overall population of MI's. I think that may have been a very important lesson to be learned in relationship to your comments earlier in terms of what should be the population be randomized. I think if one tries to start out with an overall population of post myocardial infarction patients, that it is doomed to failure, particularly if one uses some of the exclusionary criteria that have been used in some of the other trials, for example in the case of the propranolol study you were dealing with an annual first year mortality somewhere around 5 to 6% and 9.7% two years to try to show a difference in using mortality as an end point. Under that circumstance, I think it would be quite unlikely and I think that is what happened with the previous trials.

Dr. Kupersmith: I have two questions. One regards classification of drugs which was mentioned a few times this afternoon, and something that we have stressed to very little avail is that the effect of drugs on an abnormal tissue is very important. Sometimes if one studies it in that way, one can come up with surprises that one wouldn't have noted just studying it in normal tissue. In the patients we treat of course we are trying to treat abnormal tissue. The second question I have regards the number of patients that are used in trials. If one has a drug that is extremely effective in reducing VPC's, one could probably get by with the kind of studies that have been discussed today with very small numbers of patients. I wonder after all the electrophysiologic studies, also generally involve small numbers of patients and frequently the patients aren't studied very long at all. I wonder if this is considered in the approval process, the total number of patients that have been studied and the amount of time that has been studied.

Dr. Temple: You have to break this into two questions. One is, what is the evidence that the drug is an effective antiarrhythmic and you can answer that with the relatively small number of patients and a relatively small number of sites. There are additional questions that are pertinent, especially if the drug is being considered for use in not necessarily life threatening arrhythmias and that is what is it's tolerance? Does it have some long term effect that you didn't expect. The bulk of the patient exposure is really intended to evaluate safety as much as anything and of course there are other questions such as obtaining reasonable evidence of dose response, figuring out what the dose interval and other things that also require some patient exposure. The fundamental evidence that the drug is an active antiarrhythmic is often obtained from relatively small studies.

Dr. Kupersmith: So you do consider the total numbers.

Dr. Temple: We have various rules of thumb, none of which are written in stone or particularly logical. For a drug with expected widespread use that doesn't have any documented advantage in any particular situation, you ordinarily like to see something like 750 or 1000 people exposed in some setting and that is typically what you see. Now a large majority of those people are exposed in what would be called uncontrolled settings in which adverse reactions are reported carefully and you don't gain a whole lot more information that that. It does provide reassurance on surprising things like pulmonary fibrosis and things like that.

Dr. Kupersmith: It may not have been detected had amiodarone gone through the usual kind of approval process. I am not sure about that, but it seems to me that this is coming to everybody's attention after several year's of drug use. I think the antiarrhythmic drugs are a special situation though in which they are toxic drugs that are going to be used in very large numbers of patients.

Dr. Harrison: I would like to comment to your question about classification.

I think it is an arbitrary kind of thing, but if you do take the class 1 antiarrhythmic drugs, the Class I in the Vaughn-Williams classification and look at the electrophysiology in isolated cells and put that together with studies in patients, you can begin to separate them. Now whether that means anything or not, I am not sure, so I really would not like to get off on a classification discussion this afternoon. I think it would go on all afternoon.

Dr. Marcus: I would like the fundamental question of whether or not sudden cardiac death can be prevented by antiarrhythmic drugs? I have had the occasion of reviewing 100 consecutive deaths in the multi-center post-infarction program and trying to get at the cause, the etiology of the deaths in these individuals. I have been impressed by the fact that what we have called so-called sudden cardiac deaths, have been in many instances preceeded by ischemia or ischemic events or pain. In other instances they are Class IV cardiac patients who have gone into pulmonary congestion, pulmonary edema and of course death is always sudden since there is an arrhythmia which initiates death. Again, I think it is very important to realize that sudden cardiac death is not always a primary arrhythmic event.

Dr. Cohn: I'm glad you raised that because I was going to if you hadn't. I think that we sit here making some glib assumptions which are probably not warranted. One, that those patients with a lot of PVC's tend to die more frequently and therefore that the PVC is the harbinger of an electrical event which will cause death. I suspect when we take a large series of patients, and let's just look at the coronary group, you recognize that there are probably multiple ways that people can die and a primary electrical event may be only the mechanism in a small subset. If we only had a marker for which subset was going to die of an electrical event, than that would be the group that we should be treating with antiarrhythmic drugs. You can set up a

scenario which I think is very sensible that makes it clear that cardiac arrest protects you from myocardial infarction.

Dr. Harrison: What's that?

Dr. Cohn: When you have a sudden death from an ischemic episode, suppose you have an ischemic episode from which you have an arrhythmia which leads to sudden death, you will die really before you will develop an infarct and if you have an antiarrhythmic agent which protected you from the ventricular fibrillation, you may indeed go on to have a myocardial infarction rather than die. When you resuscitate the patient, the coronary artery is no longer occluded, often, I view the clot occurring secondarily to closure. You can actually recuscitate people from VF and have them survive without an infarct, whereas if they had gone ahead and not had the VF they might well have infarcted. So we can actually view antiarrhythmic therapy as potentially increasing the risk of muscle damage and perhaps death from another mechanism. So maybe all we are going to do is shift the distribution of deaths. I mean this may be a rather unusual scenario. I don't think we have a good insight into how we define sudden death and therefore we have a wastebasket when we talk about it because as Dr. Marcus points out in many of the studies, people in the early phase of an MI have been labeled as sudden death and it is unlikely that an electrical agent is going to have a major impact perhaps in that group. We also don't have a good insight into the various mechanisms that influence sudden death or the death in patients with coronary disease and perhaps platelet plugs play a role and in that group you would want to intervene with a different agent. I think that it is probably a little bit naive of us to think that if we have a drug which suppresses PVC's that if we could only give the drug in the right dose and get the right blood level that we are really going to see a change in mortality from coronary disease.

Dr. Rapaport: I would emphasize what Dr. Marcus said. That is some of the

antiarrhythmic effects of the beta blocker drugs in the BHAT study was emphasized today may well be from its anti-ischemic effect and that often ischemia may precipitate of an arrhythmia. If an antiarrhythmic drug in fact is an anti-ischemic drug as well then of course the benefit may be from this mechanism. Some weight is lended to that from analysis of our own experience. Like many groups, we have looked at patients who have recovered from MI and looked at the natural history and of great interest to me was the fact that when we did a multi-variate analysis using a logistic discriminatory analysis format, we found that the failure to give nitrates was an independent risk factor in total mortality in the year following myocardial infarction. That is to say, the bias should have favored the fact that patients receiving nitrates, you might have thought, were at increased risk, because presumably some of them might have been receiving it for heart failure, some for clinical angina before, continue to have angina afterwards, but in fact it was the failure to receive nitrates, suggesting that indeed an anti-ischemic is influencing late mortality and this may be an important mechanism.

Dr. Campbell: There is another point that is important here. I was at pains to stress that in populations you may incorporate a variety of patients who die of mechanisms other than ventricular fibrillation, which may not be amenable to antiarrhythmic therapy. I think it is highlighted particularly as Michel Mirowski has pointed out with patients who received implanted defibrillators that they do not have immortality conferred upon them, and there still are patients with implanted defibrillators who go on and die, apparently sudden deaths, but these are not deaths through ventricular fibrillation per se.

Dr. Harrison: I thought it was only the surgeons that said that we had to say that surgery doesn't confirm immortality but now we are going to have to say the same thing with internal defibrillators?

Dr. Woosley: Some of the earlier discussions this afternoon prompted me to ask Dr. Temple a question. What are the current requirements for quality control of Holter monitoring in drug trials now? Are there fixed guidelines? Are there plans for fixed guidelines?

Dr. Temple: I don't think so, our only requirement has been that there be a mechanism of quality control. The changes that we are now seeing in VPB rates are so enormous that it is difficult to imagine that the whole thing can be so bad that you will get the wrong answer. I am sure you will be off by 5 of 10% or something like that, but the changes in rates due to drugs are 70,80, and 90% and it requires imagining a remarkable level of chaos and incompetence to think that that sort of thing can be missed. Our requirement has generally been that there be some sort of quality control mechanism. We haven't tried to specifiy it.

Dr. Woosley: So, do I take that to mean that there is no requirement that all holters have to be done in one center in a given study?

Dr. Temple: No.

Dr. Smith: It is perhaps worth noting that consistent with Dr. Rapaport's hypothesis with the experience in the Norwegian Timolol trial in which not only was there a reduction in sudden death but also in re-infarction, this is not consistent with Dr. Cohn's hypothesis, but then of course, he may only have been applying that to non-beta blocker antiarrhythmics.

Dr. Cohn: That the only point that should be made is that we are dealing with a very heterogeneous disease and that we can't lump patients into a single mechanism and seek a single mechanism answer because certainly ischemia may be involved, but yet when you look at the demographic data that Dr. Bigger showed us earlier today and we have been talking about, it seems to be clear that death correlates far better with left ventricular function than it does with anatomy or ischemia. In fact if you haven't had an infarct, you probably have

more myocardium at risk for ischemia then when you have a big infarct. Yet the patients with the big infarcts and poor LV function are the ones who die, so it may be that even the ischemia mechanism that we are attracted to thinking may be the trigger. We are trying to find the trigger. Maybe the trigger is not the trigger in everybody and may only be the trigger in a small percentage of people and maybe in those the nitrates are working by virtue of an anti-ischemia effect, and so maybe Timolol is, but also nitrates improve left ventricular function, so they may be playing a role by decreasing wall stress which has perhaps another mechanical effect on the genesis of either mechanical or electrical events. It is a terribly complicated field and I am afraid we are lacking markers for mechanisms that help find our way through the path.

Dr. Reid: The deaths which occurred in those patients which have had the implanted defibrillator, have by and large been non-sudden deaths. There were 2 patients of the 8 who have died who did die suddenly. The death did occur, but in most instances was associated with LV failure, pulmonary edema, slow death. Another issue again with respect to mortality risks, I have been impressed with a number of studies in the literature. Wherein the group sets out to identify a high risk group which is undefined typically, but most of us conjure up the notion of a mortality risk of somewhere 20 to 30% perhaps, and then once the study starts, you look in both the placebo group and the treated group and you find low and behold, while there are no differences, the mortality is about 10%. I would like to know your opinion if we are entering a treatment effect simply by being in a study as opposed to receiving a placebo or an active drug.

Dr. Campbell: I think that is a difficult question to answer properly. The fact that you have observed and stated here certainly does occur. I mean the best way I know of wiping out primary ventricular fibrillation in the coronary

care unit is to study it. Basically, much of what we did in defining a high risk population reflected previous experience. I think unfortunately the time constant of our knowledge is relatively slow. When we look back at our mexiletine study at a population that we thought we would have a 20 or 30% first year mortality, but in fact had only a 10 to 12% first year mortality we were really not taking into account, advances in managing patients and the way in which our patient selection would be influenced by surgery and by the advent of beta adrenoreceptor blockade. I think this is one of the big challenges in designing the next studies. The protocol that I discussed with you here will probably take the best part of 18 months to get started, and in that time, there will be a number of new observations that have to be incorporated into new research protocols, or else, if we come out with an answer at the end of the study you will say it is very interesting but quite invalid because current practice involves giving drug x,y,or z. I think one of the great difficulties is being able to incorporate within a research protocol our advancing knowledge of cardiology.

Dr. Harrison: That is certainly true of anything from one of the original hypertension trials in Australia to the VA cooperative study on bypass surgery and most recently to the multiple risk factor intervention trial. All of those have been shown being in the trial may alter the natural history of what you think to be the natural history of the disease.

Dr. Rapaport: I want to also comment on that from another standpoint. I believe that sometimes the data upon which the original projection of what the control mortality is supposed to be doesn't really represent the study population. I think this becomes very evident when you look at this issue of post-myocardial infarction mortality. For example, in the case of the timolol and propranolol studies, the treated timolol group had a higher mortality group than the control propranolol group which obviously reflected differences

in their baseline characteristics. This came to our attention in a startling way when we looked at our mortality. In our group we had 141 people we were startled to see that our first year post myocardial infarction mortality in this consecutive series of patients was 18% or approximately 3 times the propranolol control mortality figure for one year mortality. Looking at reasons you immediately come up with a whole variety of them. For example, we had 33 patients over the age of 69 and when you look at the mortality among those first year mortality was 40%. Age is an enormously important factoras is the incidence of left ventricular dysfunction. I have already indicated the matter of nitrates and there are a whole host of baseline characteristics, some apparent and some really quite subtle that one has to take into consideration if you are going to project what will be the baseline or control population. It emphasizes the need to be careful about making universal conclusions upon the basis of exclusionary criteria that lets you end up with a very small percentage of the total initial population.

Dr. Winkle: I would like to address a point raised by Dr. Temple, and that is when you break these patients groups down into non-inducible versus inducible and you show a difference in outcome that there may be in fact differences in the patient populations and I think that indeed is true. That is the way that we analyzed our data. When we look at our EPS patients and made any assumptions about inducibility, non-inducibility and then looked at who did well and who did poorly, in fact the strongest predictor of mortality was the measure of LV function. Inducibility versus non-inducibility was an independent factor and in fact second, so there are a lot of factors. I think it is relevant to the other comments about not everybody dying post-MI just from arrhythmias.

Dr. Wyda: Assuming that a centralized sudden death trial is completed and assuming that many of the patients are successfully treated in that trial and

assuming that you have a variety of responses or successes in different drugs that are participating in that drug, do you think the F.D.A. will develop standards or guidelines for the numbers of patients, the types of data, the quality of data that would be expected to get approval for that indication? How will a sponsor get approval for their drug?

Dr. Temple: I guess I am not sure I understand the question. If someone were able to show that a particular kind of intervention presumably using what Dr. Harrison described as a drug cascade or some selection, it seems to me that would establish the principle that that way of doing business is useful. It would be impossible from a study of that kind to attribute any particular benefit to any particular drug. You would only be able to describe the process. You would also have great difficulty if the trial were successful in repeating it and you would not be expected to go ahead and reproduce the trial for each drug, or each set of drugs, or anything like that. I don't think you would be able to do it. In just thinking aloud and on the spot so don't hold me to it, I would think you would want to label all antiarrhythmic drugs to include a description of the trial and the process that was used to lead to a certain outcome and perhaps label drugs for usefulness as part of a certain regimen or approach to therapy, it would become difficult or impossible to have indications be drug specific anymore.

Dr. Wyda: You understood the question very well. You envision that even if some drugs not very useful in any patients.

Dr. Temple: You mean if they never succeeded in getting used in therapy? Well no, I think that would probably have an effect. If some drugs never met the entrance criteria and never got used, it would probably be somewhat difficult to support that.

Dr. Friday: One frustration of people participating in clinical studies using investigational drugs in patients who have PVC's and is incorporating

quinidine in the protocol as a control. I am sure everyone has had patients as Dr. Ruskin showed, where they have had 9 PVC's and after having quinidine, have then proceeded to have serious arrhythmias. I think some people have some medical questions using quinidine as a control for the drug studies, but the other question is does the does the the F.D.A. have standards for resistance or ineffectiveness of conventional therapy. Is it purely a subjective investigator bias?

Dr. Temple: We haven't tried to write down what ineffectiveness of some other standard of therapy means and it is probably worth someone trying to do it. I am not sure what the answer to that is. A good start would be having some common protocol that was used in many different emergency protocols so that people at least kept the same kinds of records and made the same sort of data available so that you would have some reason to think that refractoriness meant roughly the same thing going from one to another. I think it is a little hard to say whether you could reach effectiveness conclusions from data collected in that way anyway, but since so much data is collected that way, it seems worth trying a little better to make something out of it. I am not sure you could turn those things into adequate historically controlled trials, but at the present time, it is even hard to stir your finger into it and think of anything. It is very difficult to know what you have got.

Dr. Copen: I would like a plea to the people designing large scale clinical trials to take into consideration, minor and major side effects of the drugs being studied as well as their potential efficacy. The life of a practicing clinical cardiologist has become a nightmare of managing the minor and sometimes major complications of the drugs we have to put the patients on, and we virtually cannot take care of a patient anymore, without giving him one and sometimes two or three drugs to prevent something from happening to him. The majority of drugs we are talking about nowadays, we all know from using them

for serious conditions have all kinds of side effects and one finds oneself almost everyday talking to a patient and trying to decide whether they have to suffer being tired, depressed, run-down due to taking beta blockers or having diarrhea due to quinidine. In some of these situations, the efficacy is not great. If you look at the data that Dr. Morganroth quoted from the BHAT study, yes there is a 36% reduction in mortality, but you are really only going from 9% to 7% mortality which means that 98 out of every 100 patients I put on beta blockers post-MI are getting no benefit out of the beta blocker. Granted, I don't know who the two patients whose lives I saved are, but the other 98 could just as well do without the drug.

Dr. Harrison: You have raised some important points that we should certainly think about in design of trials and I think many of us share your experience of spending as much time dealing with the side effects of drugs as we do hopefully their therapeutic effectiveness.

Dr. Gentzkow: The question of the design of a trial of antiarrhythmic therapy and sudden death is far from an academic one in that the National Institutes of Health are indeed in the process of considering such a trial and its design. You, Dr. Harrison, presented some criteria for a study design which were very good, and Dr. Campbell offered a twist of that, namely that patients are not simply to be randomized but that people ought to be put on that therapy which was tested and found to be effective in some sense in them. I want to open that latter question. I want to open that can of worms and ask Dr. Campbell what he would suggest as a criteria for determining if that drug is effective.

Dr. Campbell: This is very difficult. If I can digress for one moment, if we were to study two or three drugs, would the patients receive them in a hierarchical system. That is they were given drug 1, if they responded to that, were they randomized to placebo or that drug or alternatively if three

drugs are involved should they be exposed to all three. My reason for digressing is that if they are to be investigated on all three compounds, the length of time in hospital is quite long. It depends very much on the criteria by which these patients are identified. If we use Dr. Bigger's data on very high rates of PVC's with complexity, then it is conceivable that a short IV investigation with an agent might determine efficacy to such a degree as to identify that drug is useful in the long term. Unfortunately, I think this may not be the case that these patients may require a control Holter tape of 24 hours and then will require some form of assessment of efficacy on that basis. I am not prepared to say what efficacy might be, with the investigational agents that might be chosen, it wouldn't be unreasonable to look for an 80% or more PVC reduction and anticipate that we would see that in patients that we would call responders. I have deliberately not gone into details and show the study design merely to be provocative and to think about a different mechanism by which sudden death and non-beta-blocking drugs might be investigated.

Dr. Harrison: I would like to comment briefly on that. The VA has also been discussing this and I was involved in their so called "cascade of drugs". If you go into the cascade, you have to make the decision about the hierarchal arangement of those drugs, but you really have to decide on the end points to which you are going to change to the next drug and that is pretty easy with toxicity but it is a lot more difficult with effectiveness. That becomes the critical question in that kind of design in the long run.

Dr. Temple: If you don't have a hierarchy and are neutral between several drugs, there seem two relatively straight-forward ways in which one could carry out that trial. One could randomize the sequence in which they are tried and then use the first one that meets the standard. That would be one way, or you could expose each patient to all of the regimens and then

randomize them to one of the successful ones and if the study was large enough, that should give you both the comparison of various drugs and the comparison of the approach with placebo.

Dr. Cohn: I would just like to remind everyone of the fact that we have another population of patients who are perhaps amenable to study of sudden death and that is the group of patients who do not have coronary disease. In cardiomyopathies, 50% of the deaths are really sudden deaths, that is suddenly dropping over from a state of stable left ventricular dysfunction. It well may be that in that group the mechanism is similar to the mechanism in coronary disease with LV dysfunction, but the beauty of this latter group, albeit there are complications as well, the mechanism seems to be very straight forward; that is, they are not probably dying from acute myocardial infarction or from closure of a coronary artery or from events that relate to platelet plugs, etc. These are electrical events, and there has been really no attempt to intervene in this population. We are dealing with a 40% mortality in one year which is higher than anything we have seen put up on slides of post-MI probably. A very fertile group perhaps to intervene and measure mortality and it may be a cleaner group to work with then the post-MI group.

Dr. Harrison: More plausible than your last hypothesis Dr. Cohn.

Dr. Cohn: All my hypotheses are plausible, even if wrong, Dr. Harrison.

Dr. Scheinman: Dr. Campbell, I just congratulate you on the protocol. I think it is too important not to do well. With regard to the ischemia limb of your hypothesis, how are you going to get at that. Are you going to look at exercise tolerance and what about the problem of spasm. I think we have been impressed with the group from Canada's report, where there was a very high incidence of sudden death in patients with spasm. Are you going to give these patients ergonovine? In other words, how are you going to get a handle on the

ischemic sudden deaths?

Dr. Campbell: I think we probably won't get a handle on that Mel. What I am hoping for is that we have some persuasive evidence, although I have shown evidence that was just as persuasive perhaps, but the evidence that Dr. Morganroth presented on beta-adrenoreceptive blocking drugs reducing mortality through an antiarrhythmic action, he based on showing a reduction of ventricular ectopic activity. If he can stand up and tell us that in those patients that showed ventricular ectopic reduction that these were the patients in whom mortality was benefited, then that would begin to put together the associations by which these drugs might operate. If that relationship doesn't exist, then I might imagine that they are acting through an anti-ischemic action as has been suggested in the discussions thus far. I made a point that in the protocol as we are discussing it at the present time, the use of concomitant beta adrenoreceptor blockade is not excluded and indeed would be encouraged. This gives rise to complications and problems, but at least is realistic and is real life. If you saw a patient post-MI probably one of your first responses would be to consider whether he would benefit or not from beta adrenoreceptor blockade and it would be wrong in our study protocol to deny him that because he was being randomized in a sudden death antiarrhythmic death drug intervention. I haven't answered your question because I don't think we can get at that limb in this particular study. I think that has to be looked at in a separate group.

Dr. Harrison: I would like to ask you another question. When you are talking about the individual patient response versus population response. It is easy to see that you may have patients that you know are suriving because you treated an acute arrhythmia, but it difficult to understand scientifically, how you know they are continuing to survive because you have them on that drug. In fact, I don't see any rationale for assuming that knowing what we

know about arrhythmias. I would like to toss that question back at you. I understand when you are treating the patient, but not when you are continuing to give prophylactic drug to that patient down the line.

Dr. Campbell: It is difficult unless you are prepared to take that patient off therapy and see that the arrhythmia still exists. It may be useful to point out that the drug which has the second biggest market in the U.K. is amiodarone and its indications are still for those arrhythmias which are life-threatening and prove resistant to other conventional therapies. Now you can only put that in perspective if you understand that we use below 10% of the antiarrhythmic therapy that you do in the United States which would suggest to me that there is an awful lot of antiarrhythmic therapy being used needlessly here or else we are denying a lot of patients benefit from therapy. Amiodarone was licensed by our Committee of Safety of Medicines, not on the basis of any controlled studies, showing its effect against life-threatening arrhythmias, but because of the stack of evidence in individual patients that this really did work and there were demands from the Committee of Safety of Medicines to show continuing efficacy and many patients had therapy withdrawn under controlled circumstances, had recurrent ventricular ventricular fibrillation and have been controlled with re-exhibition of therapy. I think that is the only way I can answer that question. You really have to be prepared to prove that the phenomenon is still going on by removing therapy.

Dr. Somberg: A question to the panel. Wouldn't one area of speeding the process up in selecting antiarrhythmic therapy would be to consider doing programmed stimulation with 3 or 4 drugs and in a high risk population and choosing which drug would be protective and then placing them out on long term therapy to try to follow mortality. The other area to address to Dr. Temple which relates to a few people back who asked the question in regard to testing and licensing of their drug for the indication of preventing a sudden mortal-

ity. For the beta blockers, my understanding is that eventually there may be a generic label, where any beta blocker, will have that indication if after 3 or 4 or 5 studies it is demonstrated that different beta blockers in post-myocardial infarction prevent sudden death. However, for all antiarrhythmic agents, wouldn't it have to be each individual agent tested since we know for instance with PES testing that one drug may work while the next one doesn't, even though they may have very similar basic electrophysiology. So when overall mortality study would probably have to be done for each individual agent to make that claim it would seem.

Dr. Harrison: He said a lot, we could almost start the day over again. Do you want to answer the question about the generic labeling for the beta blocking drugs? I once took the point of view at another meeting that all beta blocking drugs were alike and it was the beta-blocking activity that was important and I was torn limb from limb and finally scattered all over the room and after a long discussion everybody seemed to come back to that point of view. Would you comment?

Dr. Temple: That is not a question that has a knowable answer of course, so I guess that makes it policy. There certainly is no policy now that gives that indication to people who haven't carried out a trial. What seems clear is that you can't go doing placebo controlled trials anymore, probably, at least not of the same population and same time period that has been carried out so far. What we have said is that if someone wanted to carry out a trial it should be a positive controlled trial, an ideal sufficiently discouraging that I imagine no one will choose to do it. We haven't reached the question of whether other people should get that indication and you can make reasonable arguments on both sides of it. One comment on the other thing. If someone showed that a specific technique or approach to therapy was effective, it wouldn't be drug specific, so that you wouldn't have learned anything about a

specific drug other than it was one of the drugs in the study. ..... against placebo. In fact, given the relatively small likelihood that any given drug will be effective, it seems almost certain that such trials will fail which may be why they have generally failed in the past.

NEW DEVICES: PACEMAKERS IN THE TREATMENT OF ARRHYTHMIAS AND PREVENTION OF SUDDEN CARDIAC DEATH

TOBY R. ENGEL, M.D.

The strategy for pacing to interrupt a tachyarrhythmia is to interrupt a re-entrant circuit (or the pathways of recurrently excited tissue) prematurely, depolarizing portions of the heart so that the traveling tachycardia impulse is unable to travel onward, finding tissue in its pathway refractory. Thus the plan is not merely to discharge myocardium adjacent to the pacing electrodes or even a good portion of myocardium, but to reach and prematurely discharge still excitable portions of the arrhythmogenic tissue. Reaching this arrhythmogenic focus may require critical timing achieved by extrastimulation or bursts of rapid pacing, or require a large enough shock to depolarize everything simultaneously and discount the interval required to conduct from the electrodes to the focus.

However, pacing devices may cause problems. One problem to consider is the actual induction of ventricular fibrillation by inappropriate timing or disorganization of potential pathways of conduction, especially seen with bursts of rapid pacing. To safeguard against this problem requires multiple trials to insure efficacy, or the ability to countershock ventricular fibrillation in the Emergency Room or internally. Other problems to be considered in this section of the symposium include the recognition of ventricular tachycardia or fibrillation by the pacemaker, so as to insure efficacy ("forgetting to diagnose sudden death quickly being undesirable") and to insure against inappropriate firing (accidental induction of ventricular tachycardia or fibrillation). Evaluation of efficacy in treating these spurious events is difficult. Tape-recorded monitoring is of limited use because the arrhythmia is hopefully infrequent. There is inconsistent success in induction of ventricular fibrillation by routine extrastimulation techniques. Perhaps sometimes the best we can do is ask the patient to call us at intervals. If the call gets through,

we've avoided untreated ventricular fibrillation.

Parenthetically, the coronary patient receiving successful anti-arrhythmic therapy *will* die, perhaps suddenly, from his advancing coronary heart disease. In the patients subject to a recurrence of myocardial infarction, does an antitachyarrhythmia device violate the principle some hold that sudden death is good in trade for a suffering or disabling death? Should the device be limited to those who are functional except for their fear of sudden death? Does morbidity as well as mortality need to be considered in this comprehensive sense when evaluating efficacy?

However, assuming there are no appropriate discharges - and often in contradistinction to drugs or even surgery - these devices would seem neither to facilitate arrhythmias nor alter the response to other sorts of treatment. They are unique in consistently being complementary to appropriate drugs or surgery (I've sold them to patients as an insurance policy) and perhaps are indicated even when drugs or surgery do not fail or do not seem especially dangerous.

The problem of evaluation of anti-sudden-death devices does not seem to be their efficacy: if they sometimes work, that's wonderful; if the patient dies, that may not represent their failure. Two issues seem more important to me. Firstly, evaluation of their ability to detect ventricular tachycardia or fibrillation without false-positive diagnoses and without other causes for inappropriate discharge. Secondly, establishment of criteria to indicate in which patient they should be inserted. These issues, safety and indications, will now be addressed.

TRANSVENOUS CARDIOVERSION TO TREAT TACHYARRHYTHMIAS

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INTRODUCTION

Tachyarrhythmias may be treated effectively and safely with synchronized transthoracic direct current shocks (1). Further, an implantable defibrillator has been developed and used successfully in patients to terminate ventricular fibrillation (2,3). Recently, Jackman and Zipes (4) demonstrated that ventricular tachycardia could be terminated with shocks of $\leq$1.0 joule delivered through a catheter electrode placed in the right ventricular apex of dogs. Subsequently, we (5,6) reported our initial observations on the safety and usefulness of transvenous cardioversion of ventricular arrhythmias in humans. Extension of our preliminary results, including termination of supraventricular tachycardia, as well as methodology of transvenous cardioversion are discussed below.

METHODS

After written informed consent was obtained, a specially designed 10F catheter (Fig. 1) for cardioversion and defibrillation (Medtronic No. 6880) was inserted percutaneously and its tip was advanced under fluoroscopic guidance to the right ventricular apex (Fig. 2). Of note, transvenous catheter insertion through a variety of sites including the internal jugular vein, subclavian vein (supra- and infraclavicular approach) and antecubital vein resulted in no complications, even when catheters were left in place for more than one week. The catheter (Fig. 1) has two bipolar pairs of stainless steel electrodes that have a surface area of 2.5 cm^2/pair. The distal electrodes are located at the catheter tip and the proximal electrodes are located 13 cm from the tip. Separation between each bipolar pair is 5 mm. The distal electrodes are used for bipolar sensing of ventricular activation to synchronize the cardioversion shocks. The two distal electrodes coupled together form the cathode and the two proximal electrodes coupled together form the anode.

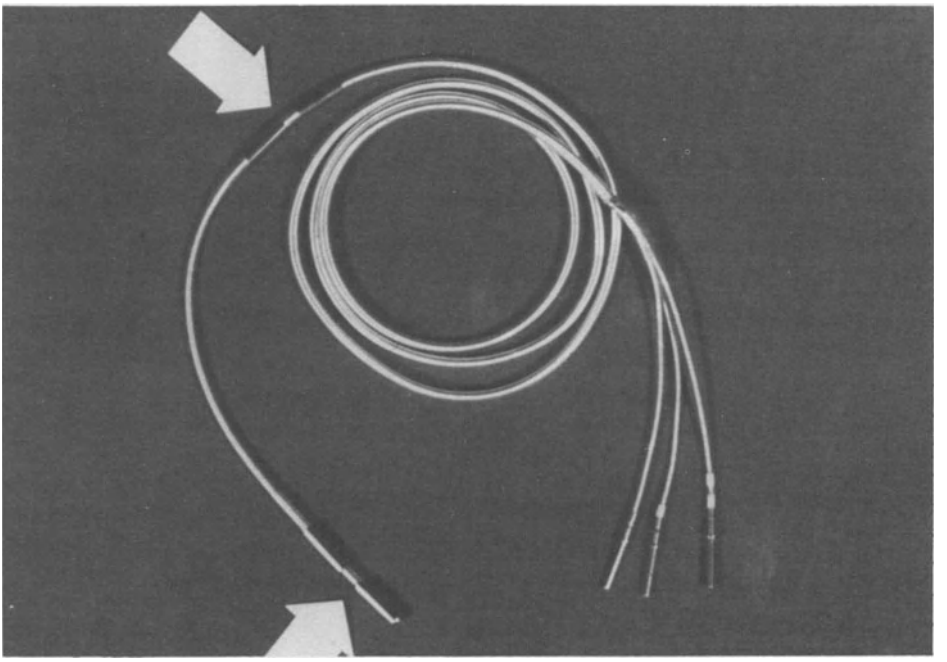

FIGURE 1. Electrode catheter. Arrows point to pairs of electrodes. Reproduced with permission from Am Heart J 103:789, 1982.

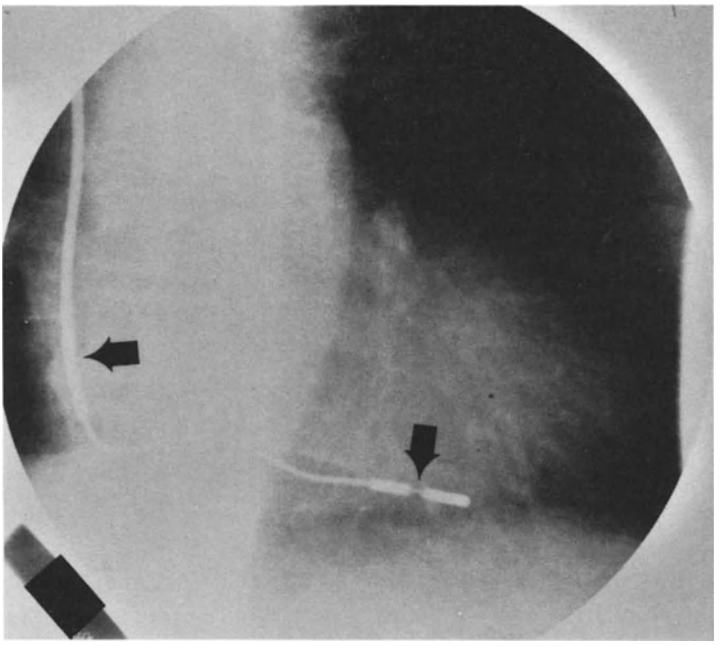

FIGURE 2. Position of electrode catheter in the heart (patient 11). Arrows point to proximal and distal electrode pairs. Note that the proximal electrode pair in this patient is at the mid right atrium.

The catheter was connected to a cardioverter (Medtronic) that delivered a truncated exponential wave form, 6 msec in duration, at multiple energy levels from 0.0075 to 3.0 joules. In one patient the catheter was connected to a conventional external American Optical (AO) cardioverter through a junction box we had built previously, and energy levels $\leq$20 joules were used for cardioversion. During ventricular tachycardia sensing of the right ventricular electrogram was accomplished through the distal electrode pair and shocks were delivered within the QRS complex. The initial shocks were selected such that the energy was below cardioversion threshold and the energy for subsequent shocks progressively was increased.

RESULTS AND DISCUSSION

Twelve male patients, aged 55 to 72 years (mean 61 years) were referred for evaluation and treatment of recurrent sustained ventricular tachycardia. No patient had a recent myocardial infarction but all had

ischemic heart disease with one or more previous myocardial infarctions. At the time of cardioversion all patients were receiving antiarrhythmic drugs. Eleven patients were awake and nonsedated during all cardioversion attempts of ventricular tachycardia. One patient requested to be anesthetized when the energy of the shocks exceeded 0.5 J during the first two cardioversion procedures. For the third cardioversion procedure, the patient was awake and unsedated.

Transvenous cardioversion terminated ventricular tachycardia in ten of 12 patients on one or more occasions with energies of 0.025 to 2.0 J using a truncated exponential waveform (Fig. 3) and 4-20 J using a damped sine wave (see below) (Table 1).

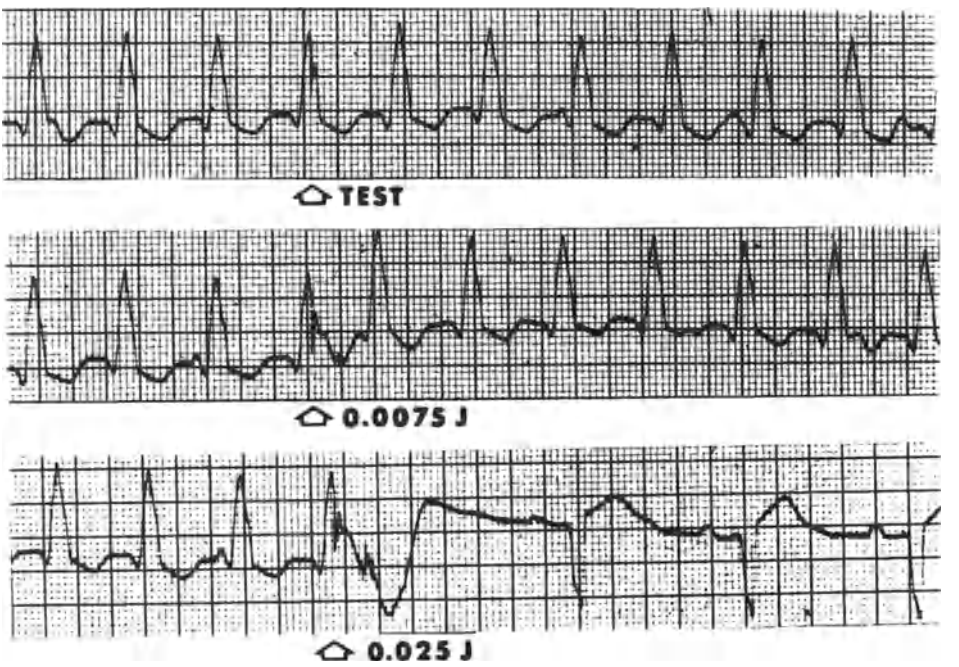

FIGURE 3. Transvenous cardioversion. Top panel: Test stimulus delivered into QRS complex. Middle panel: Subthreshold shock shortened RR interval of ventricular tachycardia but did not terminate tachycardia. Bottom panel: Threshold shock terminated ventricular tachycardia. Lead II. Reproduced with permission from Am Heart J 103:789, 1982.

Table 1.

Patient	VT Episodes Terminated	Cardioversion Threshold (joules, mean, range)
1	18	0.13, 0.075 - 0.25
2	20	0.06, 0.025 - 0.1
3	6	1.17, 0.75 - 2.0
4	2	0.16, 0.075 - 0.25
5	1	2.0, ---
6	6	0.68, 0.1 - 2.0
7	1	1.25 ---
8*	311	5.7, 4 - 20
9	0	>0.75
10	0	>2.0
11	1	1.5
12	1	0.25

* American Optical Cardioverter, see text.

In two patients ventricular tachycardia was not terminated by shocks of up to 0.75 and 2.0 J, respectively. Ventricular tachycardia resulted in profound hypotension with loss of consciousness in these two patients and therefore testing was discontinued. The tachycardia was terminated by transthoracic cardioversion (320 J) in one patient and by right ventricular burst pacing in the other patient. Shocks of 25 J terminated three episodes of ventricular fibrillation in one patient (see below) (Fig. 4).

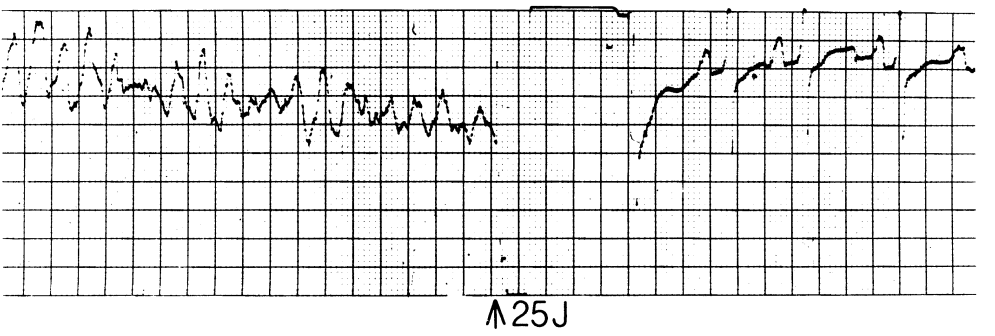

FIGURE 4. Transvenous defibrillation. A 25 J shock (arrow) terminated ventricular fibrillation. Reproduced with permission from Am Heart J 103:789, 1982.

Including subthreshold attempts, a total of 184 shocks ranging between 0.0075 and 2.0 J were delivered. Although repetitive ventricular activity occurred on several occasions, rarely did cardioversion worsen the arrhythmia. However, one patient who had undergone 18 consecutive successful transvenous cardioversions without incident deteriorated clinically. Rapid ventricular tachycardia (200 beats/min) with hypotension was present almost continuously for 72 hours. During that time he received intravenously or orally bretylium, amiodarone, lidocaine and digoxin. Balloon counterpulsation was begun to provide hemodynamic support. Synchronized transvenous cardioversion (0.075 J) in this setting transformed the ventricular tachycardia (cycle length 315 msec) to ventricular flutter (cycle length 190 msec) that was terminated by a transthoracic shock of 320 J. Shortly thereafter, a conventional synchronized

transthoracic shock of 50 J precipitated ventricular fibrillation that was then defibrillated with a 320 J transthoracic shock. Because the cardioverter has a maximum output of 3.0 J, termination of ventricular flutter or ventricular fibrillation was not attempted transvenously during these episodes. Subsequently, the catheter electrode was connected to a standard cardioverter/defibrillator and the next three episodes of spontaneous ventricular fibrillation were terminated by a 25 J shock delivered transvenously (Fig. 4).

Another patient had six episodes of sustained ventricular tachycardia successfully terminated by 0.1 J (one episode), 0.25 J (one episode), 0.5 J (two episodes), 0.75 J (one episode) and 2.0 J (one episode). The catheter position probably was not stable and the shock synchronized at different points in the QRS complex (Fig. 5). Shocks in the midportion of the QRS complex terminated the ventricular tachycardia with none or one repetitive response (panel A). Shocks of equal intensity in the latter portion of the QRS complex (panel B) sometimes failed to terminate the ventricular tachycardia. A shock delivered slightly later in the QRS complex, after termination of the absolute ventricular refractory period and during the early portion of the vulnerable period (panel C), initiated ventricular flutter/ventricular fibrillation that promptly was terminated by transthoracic cardioversion (panel D).

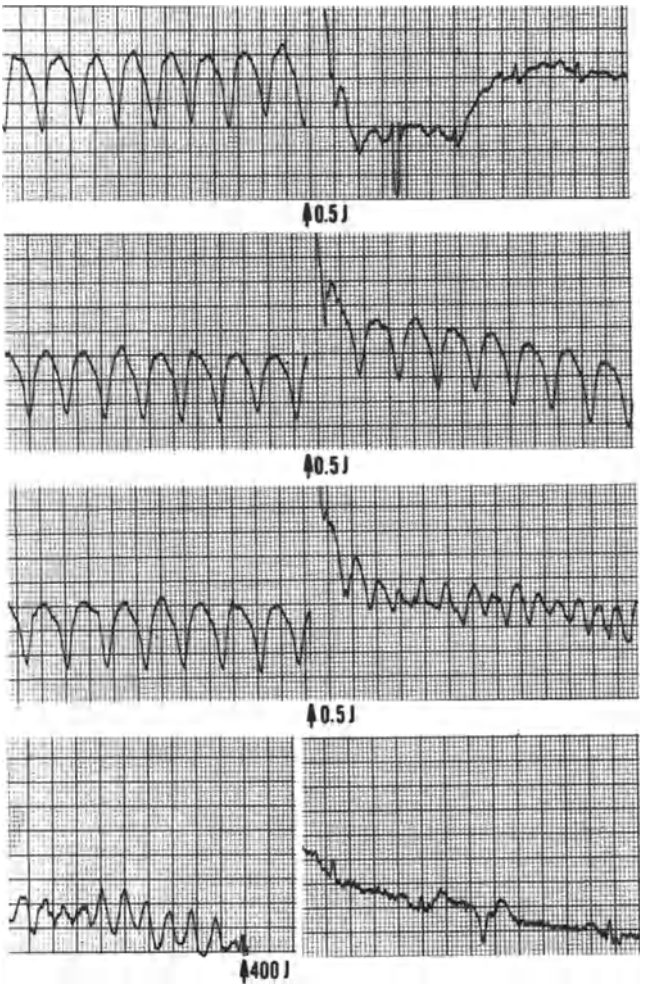

FIGURE 5. ECG rhythm recordings from a patient showing termination of a ventricular tachycardia with 0.5 J in panel A, (top), failure to terminate ventricular tachycardia in panel B, initiation of ventricular fibrillation in panel C and termination of the ventricular fibrillation with an external shock of 400 J in panel D, (bottom). Reproduced with permission from Am Heart J 104:163, 1982.

Atrioventricular dissociation occurred during all episodes of ventricular tachycardia; thus, there was random delivery of shocks in relation to atrial systole. Nonetheless, only 5 shocks caused repetitive

atrial responses. In one patient a shock of 0.25 J initiated atrial fibrillation but did not stop ventricular tachycardia (Fig. 6). Subsequently, a shock of 1.0 J terminated both atrial fibrillation and ventricular tachycardia.

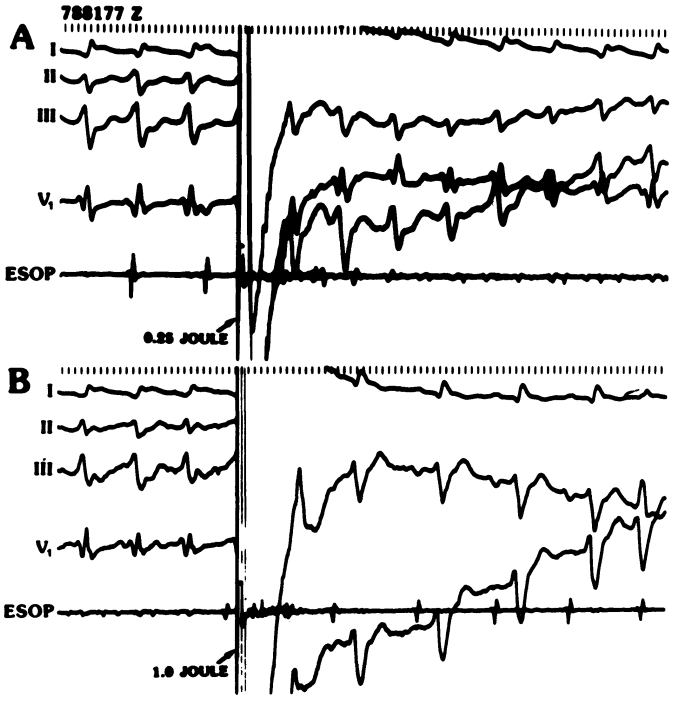

FIGURE 6. Initiation and termination of atrial fibrillation. The top four tracings on both panels are ECG Leads I, II, III and V_1 and the bottom tracing is from an esophageal (Esop) lead. Panel A: a shock of 0.25 J does not terminate ventricular tachycardia (VT) but initiates atrial fibrillation. Panel B: VT and atrial fibrillation are terminated with a shock of 1.0 J. Time lines = 50 msec.

We (6) and others (7) have demonstrated the usefulness of transvenous cardioversion in patients who require repeated cardioversions. For example, a patient was referred to us for treatment of drug refractory recurrent ventricular tachycardia on the same day that another patient presented with a similar problem. We connected the catheter electrode to a conventional external American Optical (AO) cardioverter through a junction box we had built previously, just in case we needed to treat two patients at the same time. He ultimately died with refractory cardiogenic shock in an agonal slow ventricular rhythm with electromechanical dissociation. Prior to his hemodynamic collapse, he had received 311 cardioversions in a 12 hour period. We synchronized the shock from skin electrodes through the AO cardioverter and delivered the shocks from the standard AO cardioverter through the transvenous catheter electrode. Naturally the precise voltage setting on the meter of the AO cardioverter cannot be determined with the degree of accuracy we were able to achieve using our specially made cardioverter. However, 245 episodes of ventricular tachycardia were terminated with 4 J, 45 episodes with 8 J, and 21 episodes with 20 J. One shock in the latter range accelerated the ventricular tachycardia from 140 to 210 per minute, but otherwise there were no problems.

Complications of catheter insertion did not occur in any patient. Shocks of $\leq$0.5 J were tolerated well; patients either did not feel the shock or described it as a "giant hiccough" or light blow to the chest (most likely due to diaphragmatic or intercostal muscle contraction). However, shocks >0.5 J commonly caused substantial discomfort, and patients often described the feeling as a "kick in the chest".

Therapy for most patients who have ventricular tachycardia involves using drugs, although in many patients no drug or drug combination can be identified that prevents recurrence of tachycardia (8,9). Further, drugs that appear to be effective during short observation periods may actually be arrhythmogenic (10). Alternative therapies include surgery in a selected subset of patients (11,12,13) and a variety of pacing modalities. The latter have been of limited value, primarily because competitive ventricular stimulation may speed the rate of the ventricular tachycardia and produce ventricular flutter or ventricular fibrillation (14,15,16,17). Conventional synchronous transthoracic cardioversion is the most effective and safest form of electrical therapy to terminate

ventricular tachycardia[1], but has obvious limitations for chronic application. The impetus for this study was to develop a therapeutic approach that was as safe and as effective as synchronous transthoracic cardioversion but could be used chronically, eventually as totally implanted system.

Transvenous cardioversion terminates ventricular tachycardia in patients with very small amounts of energy. It is possible that antiarrhythmic drugs in these patients influenced the cardioversion thresholds to some degree. Other factors that may affect threshold are the size of the heart and origin of the ventricular tachycardia in relation to electrode position. Future developments in catheter electrode design and the waveform of the shock may reduce energy requirements further.

It is possible that transvenous cardioversion may be used for some patients who have recurrent episodes of supraventricular tachycardia. In animals (4) several episodes of atrial flutter or atrial fibrillation were terminated by delivering a transvenous shock of 1.0 J. In the present study, 1.0 J terminated atrial fibrillation.

Transvenous cardioversion has multiple potential applications. For example, the catheter electrode connected to an external unit can be used on a temporary basis for the patient who has frequent recurrences of ventricular tachycardia or ventricular fibrillation, thereby avoiding repeated chest trauma and the need of anesthesia for cardioversion if thresholds are low. The catheter electrode can be used also to pace the heart. Thus, during electrophysiologic studies in patients, pacing-induced ventricular tachycardia or ventricular fibrillation can be terminated with the same catheter electrode. As a permanent implant, the size of the generator could be relatively small and longevity relatively long, compared to the automatic implantable defibrillator,[3] because of the reduced energy requirements. A transvenous cardioversion system will have the additional advantage of not requiring a thoracotomy for implantation. It is also possible that transvenous cardioversion may be easier to test and use than pacing modalities. The latter generally require in-depth electrophysiologic evaluation of the patient to determine precise electrophysiologic parameters--i.e., number of

drugs that may alter the parameters of pacing-induced termination markedly. Finally, since in many patients, episodes of spontaneous ventricular fibrillation are preceded by ventricular tachycardia(18), the former may be prevented entirely by cardioverting the latter. Conceivably in the future the ideal implantable device will be capable of transvenous cardioversion and, if that fails or if ventricular fibrillation is precipitated, it will then deliver a defibrillating shock.

As with any device that delivers electricity to the ventricle, transvenous cardioversion is not without some risk. This is not unexpected in light of the known potential arrhythmic complications of transthoracic cardioversion (19). All those precautions used with transthoracic cardioversion regarding a precisely synchronized shock should be employed with transvenous cardioversion.

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THE ROLE OF PERMANENTLY IMPLANTED PACEMAKERS IN THE THERAPY OF RECURRENT TACHYARRHYTHMIAS

Griffin, Jerry C., M.D.

In 1967 Haft, et al,(1) described the successful termination of atrial flutter using pacing stimuli. Since that time, others have demonstrated the termination of a number of reentrant tachycardias by various pacing techniques. In fact, the ability to terminate a tachycardia with pacing stimuli has become a part of the clinical definition of reentry.(2) Although this chapter will focus on the use of permanent pacemakers for the termination of tachycardias, other strategies for the use of pacing in patients with tachyarrhythmias exist. The prevention of bradycardia by pacing at normal rates or continuous rapid pacing may prevent tachycardia in selected patients.(3,4) Occasionally, pacing may allow the substitution of a more easily managed tachycardia, such as the conversion of atrial flutter to atrial fibrillation.(5,6) Finally, pacemakers allowing serial, non-invasive, electrophysiologic testing may be used in the long-term follow-up of patients receiving primary pharmacologic or surgical therapy.(7)

Tachycardia Termination by Pacing Stimuli

There are three basic stimulus patterns for termination. The first is the application of single or pairs of extrastimuli. These may be externally initiated and randomly applied as with the application of a magnet to an ordinary single chamber inhibited pacemaker.(8) This type of response has also been automated allowing the pacemaker to automatically recognize a tachycardia and revert to the asynchronous pacing mode, the dual demand pacemaker.(9) Another step in the automation of this approach to termination is the scanning pacemaker which allows single or dual programmed extrastimuli to scan a selected portion of the relative refractory period of the chamber involved, each precisely timed from the preceding beat.(10,11)

Perhaps the most widely used technique for tachycardia termination is a burst of rapid pacing.(12,13) Burst pacing is intrinsically asynchronous to the tachycardia, but may be initiated in a synchronous fashion. Burst stimulation is most effective at rates 30 to 50% greater than the tachycardia rate. Finally, A-V sequential pacing techniques particularly those utilizing simultaneous or near simultaneous atrial and ventricular stimulation, have been reported.(14,15,16) These have been particularly effective in atrioventricular and A-V nodal reentrant tachycardias.

Burst pacing is generally more effective in a wider range of arrhythmias than random or programmed extrastimuli. Faster tachycardias, with rates in excess of 180 per minute, are seldom effectively terminated by single or multiple programmed stimuli, but burst pacing may be effective at tachycardia rates much higher than this. However, burst pacing may be accompanied by increased risks of adverse consequences. A comparison study has demonstrated a higher incidence of atrial fibrillation in patients with supraventricular tachycardia undergoing burst termination compared to various types of programmed stimulation.(13) The consequences of fibrillation and/or acceleration of tachycardia rate are minimal in most patients with SVT, but may occasionally be significant, such as in the presence of a rapidly conducting accessory pathway. Obviously, acceleration/fibrillation is a very serious hazard in ventricular applications. While the risk of acceleration and/or fibrillation is low relative to the number of attempts at termination, a significant number of patients will have acceleration or fibrillation at least once during multiple attempts of termination.(12) We can identify some of the factors associated with an increased risk of acceleration-such as faster tachycardias, faster burst rates for termination, and the presence or absence of antiarrhythmic drugs. However, other factors such as the amount of pacing energy applied, the polarity of the stimulating current, and the synchronization of the initial stimulus in the burst to the preceding spontaneous beat may also play a role.

Therefore, various modes of pacing termination may be applied safely as a long-term therapy in patients with SVT after the mechanism

and functional characteristics of the tachycardia are determined. In patients with ventricular tachycardia, the risk of an adverse response precludes pacing therapy except after the most strenuous evaluation and in the most refractory of patients.(17)

Tachycardia Identification

Currently three techniques exist for the recognition of a tachycardia. Perhaps the most accurate system is tentative recognition of tachycardia by the patient due to the occurrence of symptoms and electrocardiographic confirmation by a physician. After satisfactory tachycardia identification, the physician can then initiate a pacing sequence designed to terminate the arrhythmia. Although this method is cumbersome for ambulatory patients, it is accurate and relatively safe even in those patients prone to acceleration of tachycardia or fibrillation. It allows the immediate application of backup measures such as resuscitation and external cardioversion if acceleration or fibrillation should occur. In addition, it provides confirmation of the presence of tachycardia or termination for those patients who have difficulty in being certain whether an abnormal rhythm is present or absent. Disadvantages include the time necessary to reach a hospital or emergency room and the lack of physicians adequately trained in tachycardia termination techniques.

If the patient is reasonably accurate in his perception of the cardiac rhythm and if the consequences of an adverse response to termination are innocuous then the patient may be trained to perform his own tachycardia termination. This reduces the time lag in applying therapy after the onset of tachycardia and decreases the dependence of the patient on the physician. It still leaves, however, a significant residue of symptoms and the requirement that an external transmitter, magnet, or other device be readily available at all times should tachycardia occur. This may lead to anxiety and psychological dependence in some patients. Careful evaluation is necessary to insure that the patient is consistently able to correctly identify his cardiac rhythm, and apply the corrective measures. This technique is of little use in the patient rapidly disabled by an arrhythmia.

Finally, the tachycardia may be identified by the pacemaker and the terminating sequence automatically initiated. This provides the most rapid termination of the arrhythmia with the least patient awareness.

Presently, all automatic pacemakers define tachycardia as the occurrence of electrical signals identified as R or P waves occurring at intervals sufficiently short to meet pre set criteria for tachycardia and sufficiently long not to be designated as noise. A change in voltage from the electrode is defined as an R wave if the signal meets certain pre set criteria for amplitude and frequency content. The raw electrogram is filtered by the pacemaker eliminating low and high frequency signals, so that only the electrogram of local depolarization is preserved. This filtered signal is then tested for amplitude and if sufficient the waveform is identified as an R or P wave depending on the placement of the electrode. The site and type of electrode may be critical in allowing the pacemaker to make an accurate distinction between local and distant depolarization, particularly in the atrium.(18) Due to the disproportionate muscle mass, ventricular activity may appear quite prominently in the atrial electrogram from electrodes placed in the coronary sinus or from unipolar electrodes in the right atrial appendage. Bipolar high right atrial electrodes present the pacemaker with the best opportunity for making the distinction between local and distant depolarization. Therefore, this type of electrode is recommended for use with automatic tachycardia terminating pacemakers in patients with SVT.

Most of the difficulties encountered with automatic implantable tachycardia terminating pacemakers for supraventricular tachycardia result from problems with sensing. Undersensing, oversensing, and erroneous identification of tachycardia have been noted. Oversensing, or the identification of signals other than local myocardial depolarization may result in the pacemaker counting twice during each cardiac cycle. This results in the false identification of tachycardia when the heart rate is sufficiently rapid that the longest interval between two events is shorter than the tachycardia criteria. Undersensing is not uncommon with atrial pacemakers, since the average atrial electrogram is much smaller than that from the ventricle. In

addition, the electrogram during supraventricular tachycardia or from premature atrial beats may vary from that of normal sinus rhythm. In some supraventricular tachycardias such as A-V nodal reentry, superimposition of atrial and ventricular events may also significantly compromise detection of the local atrial electrogram. Occasional undersensing of normal sinus or premature beats may cause the initiation of tachycardia in those pacemakers with backup pacing. If the escape interval of backup pacing is longer than the spontaneous interval and sensing does not occur, a stimulus may be inserted shortly after the spontaneous beat. This stimulus may fall within the initiation "window" and produce tachycardia. Sensitivity programmability is a critical feature for pacemakers which automatically identify tachycardia and initiate a terminating sequence. In such patients, if the tachycardia can be induced, sensitivity can be appropriately adjusted for both sinus rhythm and supraventricular tachycardia, so that both oversensing and undersensing are minimized or eliminated.(19)

Sinus tachycardia also presents a problem for the current generation of automatic devices. They use only the rate of local depolarization; and no estimate is made as to whether each beats is normal or abnormal. Therefore, sinus tachycardia at rates exceeding the tachycardia criteria of the pacemaker will be identified as an abnormal tachycardia and termination attempted. This can be minimized by adjusting the tachycardia criteria to the best compromise rate between the two. The misidentification of sinus tachycardia is usually of little consequence in patients with supraventricular tachycardia, but may be a critical short- coming of automatic pacemakers in the management of patients with ventricular tachycardia.

Increasing complexity of pacemaker electronics will hopefully allow greater sophistication in the detection and differentiation of the local electrogram in patients with tachycardias. Identification schemes based on characteristics of individual electrograms or changes in timing characteristics between atrium and ventricle or localized sites in either chamber may allow more precise identification of pathologic tachycardia and assist in their differentiation from sinus

tachycardia or supraventricular tachycardia in patients with ventricular tachycardia terminating pacemakers.(17)

Evaluation of Tachycardia Patients for Pacing Therapy

Even though successful long-term therapy is well documented,(20-27) at present the application of pacing in patients with supraventricular tachycardia is frequently reserved for those either refractory to medical therapy or in whom a surgical therapy is either not available, contraindicated or refused by the patient. In fact, however, pacing therapy of some type may be considered in many patients with supraventricular tachycardia of reentrant mechanism. The effectiveness of various pacing modes and electrode sites must be evaluated in each individual patient. Caution should be used in the application of pacing therapy in patients with A-V reentrant tachycardia in which there is the capability for rapid anterograde conduction via an accessory pathway. This may allow 1:1 conduction at excessive ventricular rates in those patients in whom rapid atrial burst termination is used, or allow rapid conduction to the ventricle following the inadvertent initiation of atrial fibrillation. As noted above, pacing techniques are effective in patients with ventricular tachycardia as well, and the utilization of pacing as a primary form of treatment has been reported.(17,26,28-31,32) However, due to the tendency for tachycardia acceleration or fibrillation these patients must be carefully selected and automatic devices used only with the greatest of caution.

Little data exist as to the frequency of pacemaker vs medical or surgical therapy or comparing the effectiveness of pacing to medical or surgical therapy. We evaluated 13 consecutive patients presenting with refractory supraventricular tachycardia. Burst pacing was effective in ten patients and partially effective in two. Eight patients were treated with medical or surgical therapy and five underwent the implantation of an automatically responding multiprogrammable burst pacemaker. An excellent response has been observed in all five patients for nearly three years after pacemaker implantation. Fisher and colleagues (17) reported the application of pacemakers for arrhythmia termination in 17 of 160 patients presenting

with ventricular tachycardia. Thus, it would appear that cardiac pacing may be a effective therapy in patients with reentrant tachycardias particularly if supraventricular. We may be rapidly approaching a time when pacing is considered an alternative to effective medical or surgical therapy in patients with recurrent symptomatic supraventricular tachycardia.

For the patient being evaluated for pacemaker therapy of supraventricular tachycardia, several important questions must be answered in order to determine if pacing is a viable alternative:

Is the arrhythmia symptomatic? Is pacing termination effective? Is medical therapy adequate? What is the burden of medical therapy in terms of cost, dosing frequency, side effects and risks? What is the level of patient reliability and compliance with a medical regimen? What is the role of surgical therapy, particularly the application of curative procedures such as accessory pathway ablation. Are newer techniques such as non-surgical ablation of the A-V conducting system an alternative?

Once pacing therapy is selected the physician must decide whether an automatic or externally triggered device is preferred. Patient reliability, particularly in terms of arrhythmia detection and awareness, is important for triggered devices. Arrhythmias which are immediately disabling may be best treated with an automatically responding device. In those patients in whom arrhythmia termination requires monitoring due to a tendency toward acceleration or fibrillation, an externally triggered device is obviously preferable. In some patients, marked variation in tachycardia rate may make the selection of a single, reliable terminating pattern difficult with present day non-adaptive pacemakers. In patients in whom the sinus tachycardia rate frequently exceeds the rate of the pathologic arrhythmia, externally triggered pacemakers may be preferable.

There is currently available, either in distribution or clinical investigation, a wide variety of specific implantable devices for tachycardia therapy. Most ventricular inhibited pacemakers may be converted by a patient or physician to the asynchronous mode simply by

the application of a magnet. Other externally activated devices are available with and without an internal power source and are able to provide everything from a simple burst to complex patterns of stimualtion. Automatically activated pacemakers are available, supplying random asynchronous pacing, coupled scanning and bursts of rapid pacing. These may be either programmable or non-programmable. Finally, AV sequential pacemakers are also available for investigation.

Table 1. Pacemakers for Tachycardia Therapy

- Externally activated
  - Externally powered - RF coil
  - Internally powered
    - Synchronous response to external signal
      - Magnet activated

- Automatically activated
  - Single or dual stimuli
    - Scanning
    - Dual Demand
  - Bursts of rapid pacing
    - Programmable
    - Non-programmable

  - A-V sequential

Future Trends in Pacing for Tachyarrhythmias

Hopefully, we are only in the most primitive stages of what appears to be an exciting and useful therapeutic approach. However, one might predict some of the features of future pacemakers for tachycardia therapy. They would be capable of both tachycardia induction and termination so that adequate testing can be done. They would also obtain and store certain arrhythmia monitoring data in order that more optimal programming adjustments could be made. These pacemakers would be able to adapt automatically to changes in the tachycardia providing

the most suitable mode of termination for the particular rhythm with which it is confronted. Tachycardia identification would be done by the pacemaker and be based on multiple criteria, allowing a precise identification of pathologic rhythms. Finally, these devices would have fully programmable bradycardia pacemaker function and sufficient programmability of all functions to ensure optimal long-term performance.

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CLINICAL EVALUTAION OF AN IMPLANTABLE AUTOMATIC CARDIOVERTER DEFIBRILLATOR

PHILIP R. REID, M.D.

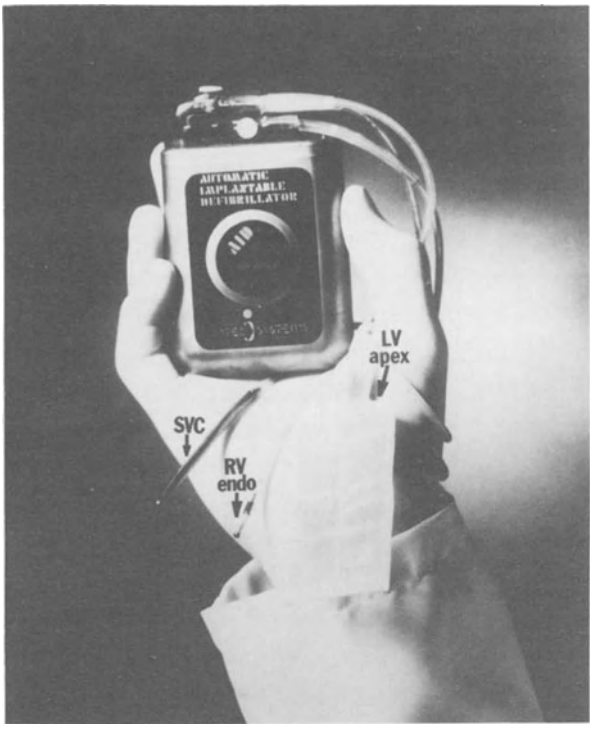
INTRODUCTION

The implantable automatic defibrillator (IAD) was originally conceived to convert only ventricular fibrillation (VF).[1] Following successful testing in animals, the first clinical implantation in February 1980 successfully employed a similar design.[2] However, it soon became apparent that ventricular tachycardia (VT), and not VF, was the major rhythm disturbance which initially produced syncope in patients at risk of sudden cardiac death. This realization prompted major design modifications to be undertaken and resulted in a implantable automatic cardioverter-defibrillator (IACD) which was initiated in clinical trials in April, 1982.

General Features of the Implantable Automatic Cardioverter-Defibrillator

The IACD (figure 1) is a device with external dimensions of 7.1 x 11.1 x 2.54 cm weighing 290 gms and an internal volume of 162 cm^3 with a specific gravity of 1.8. The case is constructed of titanium, hermetically sealed and contains a special lithium battery capable of charging 2 capacitators to approximately 700 volts in 7-9 seconds.

Although the cardiac rhythm is continuously monitored, there are two criteria required for causing the IACD to charge and discharge the capacitators. One criterion is the ventricular rate. The second criterion is termed the probability density function (PDF).[3] The PDF is a measure of the amount of time the cardiac signal spends away from a zero-potential baseline. As this time increases the PDF becomes



satisfied. As a practical consequence a signal in sinus rhythm creates relatively frequent zero-potential times (e.g. PR segment, ST segment and T-P segment) compared to a signal in VT or VF where relatively little time is spent at the zero-potential point.

There are two electrodes which serve for both defibrillation and sensing the PDF: one is an intravascular catheter positioned in the superior vena cava near the right atrial junction. The second electrode has the form of a flexible rectangular patch and is placed over the apex of the LV. Either a bipolar right ventricular endocardial catheter or intramural bipolar electrodes serve for rate detection and R-wave synchronization. Input signal compensation is provided for wide amplitude variations, however, the minimum voltage required for sensing is approximately 0.1 mv. When both the PDF and rate criteria are satisfied,

the device delivers a truncated exponential pulse of approximately 6 ms across the SVC and LV patch electrodes. The initial discharge is approximately 25 joules but the IAD can recycle three times with the strength of the last three pulses automatically increased to 30 joules. All discharges are synchronized to the detected onset of ventricular depolarization.

The present IACD provides several new features which can be monitored noninvasively following implantation: using a strong external magnet and detector (AID check B^R) applied over the pulse generator in the subcutaneous periumbilical area, the number of delivered pulses and capacitator charging time can be measured. When the IACD is activated using the magnet, the test load is delivered through an internal resistor and the patient feels nothing. If the magnet is held in place above the implanted device, an audible beeping tone is emitted synchronous with the detected R wave which permits a rapid check of the R wave sensing function. In addition, the magnet may be used to completely inactivate (or reactivate) the device. Radiodense insignae are incorporated within the IACD which permit easy identification.

The pulse generator can deliver up to 100 discharges or remain in a continuous monitoring function for up to three years before requiring replacement. This is accomplished under local anesthesia in a fashion quite analogous to permanent pacemaker exchange. By periodically performing a noninvasive magnet test one can electively stage pulse generator replacement by noting a progressive increase in the time required for the battery to fully charge the capacitators.

Patient Population

As of September, 1982 a total of 48 patients (primarily at Johns Hopkins) have received either the older IAD or the newer IACD. Nineteen patients have received the IACD and the 12 patients who received implants at the Johns Hopkins Hospital will serve as the focus for this discussion.

The criteria for IACD implantation require the patient to have experienced at least one out-of-hospital episode of sudden cardiac death associated with ventricular tachyarrhythmias but unassociated with an acute myocardial infarction; or the patient may have sustained ventricular tachyarrhythmias induced during programmed electrical stimulation (PES). In addition, the patient must be mentally capable of making the decision for implantation and have no other diseases which would likely cause death within 12 months. We also require these patients to have failed conventional antiarrhythmic agents. The use of investigational antiarrhythmic agents does not preclude implantation of the IACD. Some antiarrhythmic agent is, in fact, generally employed to reduce the frequency of clinical events.

A summary of the clinical features in the 12 patients who received the IACD is presented in Table 1.

Table 1

N = 12: 7 male; 5 female
Age = 60 ± 8.5 (S.D.) yrs (range = 48-75)
Episodes of Sudden Death: 3.0 (range 1 to > 10)
Prior Antiarrhythmic Drugs: 5.0 ± 1.6
Primary Diagnosis:
    Coronary Disease = 11
    Prolonged QT = 1
Clinical CHF Class III or IV: 4
Ejection Fraction: 0.34 ± 0.13

These characteristics are quite similar to our larger IAD population except for the lack of nonischemic cardiomyopathy which usually accounts for approximately 25%, with coronary artery disease being the most prevalent at approximately 70-75%. We have not yet encountered a patient who did not have some distinctly abnormal cardiac function (this includes patients with the prolonged QT syndrome). As would be expected in a patient population of this type, ventricular function is usually severely imparied and is reflected in the average ejection fraction of 0.34.

Pre-Operative Evaluation

This is required in all patients and includes Holter monitoring, exercise testing, measurement of antiarrhythmic drug levels, cardiac angiography and PES. These results are used to not only document suitability for IACD implantation but, equally important, to help in management of such things as congestive heart failure and angina. In addition, many patients require other cardiac surgery to be performed as part of their general cardiovascular management. The other surgery performed has included coronary artery bypass, mitral valve replacement, aneurysmectomy, subendocardial resection and pacemaker implantation. The surgical approach[4] is dictated by the type of surgery required; however, if only IACD implantation is required we attempt to use a subxiphoid incision which reduces post-operative recovery time.[5]

Post-Operative Results

Of the original 12 patients who received both the IACD leads and pulse generator, one died in the post-operative period. This patient developed cardiogenic shock and VT. Prior to the patient's death we documented proper IACD function during spontaneous VT. The general characteristics of the IACD implanted in these 12 patients are summarized in Table 2.

Table 2

IACD Rate Min.: 160 ± 6 (S.C.) BPM
Energy (1st Dischg): 24 ± 2 joules

The average rate minimum of 160 BPM represents a great reduction in the required VT rate when compared to older IAD unit which needed a minimum of approximately 175 BPM and lacked the accuracy of the newer IACD.

Post-Operative Evaluation

As a part of the IACD management, we require a post-operative electrophysiologic study. PES is used not only to document proper IACD function but also to evaluate the results of any changes in drug therapy or surgical procedures such as subendocardial resection. The results of the IACD

function during post-operative testing are summarized in Table 3.

Table 3

Magnet Test (sec): 7.5 ± 0.8 (S.D.)
IACD Charge Time (sec): 7.3 ± 0.5
Induced Tachyarrhythmia:

VT: 10
VF: 1

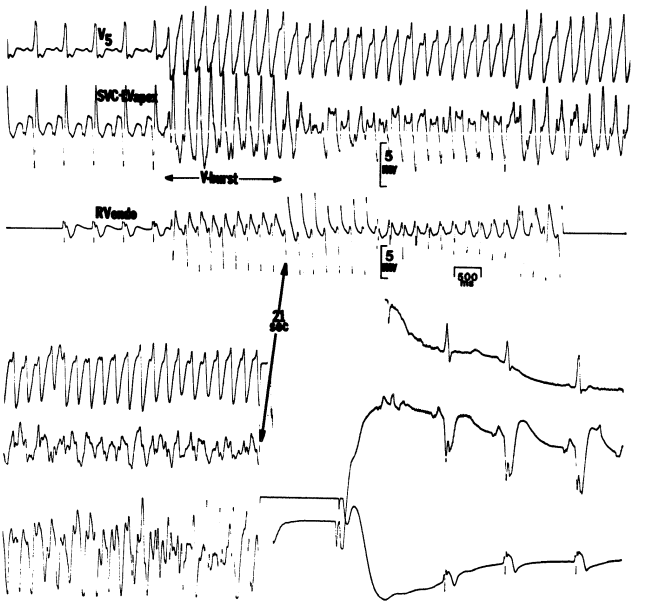
VT Rate (BPM): 200 ± 44 (Range = 160-300)
Rate Detector Lead Voltage:

Sinus: 14 ± 4 mv
VT: 22 ± 8 mv

Total Time to Conversion (sec): 17.9 ± 4.2

Prior to actually attaching the leads to the pulse generator. a magnet test (as described earlier) is performed and then the actual IACD capacitator charging time is again measured during the induced tachyarrhythmia. As shown in Table 3, there is very close agreement between the magnet testing time and the charge time during VT. The total time from onset of the tachyarrhythmia until IACD discharge averaged approximately 17 seconds in these 11 patients. This time includes the time for rhythm recognition and capacitator charging time. With the dishcharge of the IACD, the pre-induction arrhythmia was re-established in all 11 patients with a single discharge and there were no complications encountered. Table 3 also emphasizes an important feature in these sudden cardiac death survivors: The induced rhythm was VT in 10 with VF in only one (the patient with the prolonged QT syndrome).

An example of one post-operative PES study is shown in Figure 2 as a noncontinuous recording. The upper trace is surface lead V_5. The second trace is from the bipolar lead which is used to sense the PDF and deliver the cardioverting pulse (SVC-LV apex). The third trace is recorded from the ventricular lead which is used to count the rate and synchonize the pulse (RV endo). Sustained VT was induced from sinus rhythm using a burst of 10 rapid pacing pulses.



Twenty-one seconds later the IACD delivered 25 joules with restoration of sinus rhythm within 1.5 seconds after the discharge. In contrast to the SVC-LV apex lead, one can appreciate the accuracy of rate counting when comparing the surface lead to the IACD rate-detecting lead. The average voltage measured (Table 3) during both sinus rhythm and VT in 10 patients is well above the required IACD minimum of 0.1 mv.

Table 3 also demonstrates the wide rate range of ventricular tachyarrhythmias to which the IACD was found to appropriately respond: VT as slow as 160 BPM through VF were all effectively cardioverted. While the IACD is capable of recycling up to three times, all of these patients were managed with a single discharge which may reflect lower energy requirements provided by a synchronous pulse delivery.

DISCUSSION

These results are from a relatively small group of patients but serve to extend our previous reports that an implanted device such as this can safely and effectively manage life-threatening ventricular tachyarrhythmias. Furthermore, the IACD, in contrast to the older model IAD, provides automatic cardioversion of a wide spectrum of potentially lethal rhythm disturbances ranging from relatively slow VT through VF.

While the IACD provides several technical improvements over earlier models, the most significant are probably the accuracy of rate counting and the ability to deliver an R-wave synchronous pulse. If these results are confirmed in a larger series, they may permit a lowering of pulse energy and consequent reduction of pulse generator size or battery life extension.

While we consider these preliminary results as encouraging, several potential limitations must be kept in mind: 1) as a characteristic feature of antiarrhythmic drug effects, VT which is not effectively suppressed may be significantly slowed. While we consider the IACD to be complementary to other forms of management, if the VT rate falls below the IACD rate minimum, the device cannot be expected to discharge. Thus, attention to concurrent drug therapy becomes increasingly important in IACD patients; 2) while the IACD provides accurate rate detection, one should anticipate the potential for "spurious" discharges under certain conditions such as an intraventricular conduction-defect (IVCD) in the presence of a supraventricular tachycardia (PSVT). In this situation both the PDF and rate minimum could be satisfied leading to IACD discharge. Although in some instances, e.g. rapid atrial fibrillation with an IVCD, electrical cardioversion might be clinically desirable, it, nevertheless, is not VT. This is one of our reasons for using pre-operative and post-operative stress testing. In our experience, it is distinctly unusual for these patients to attain an exercise heart rate above the IACD rate requirement. However, recognition

of this possibility or the potential for PSVT can permit the appropriate addition of drugs to increase AV nodal conduction time and obviate this potential complication. Five patients in the present series had an IVCD with QRS durations exceeding 120 ms and none have had inappropriate discharges; 3) several of our patients have required permanent ventricular pacemakers and the possibility exists that inappropriate rate counting could occur from the IACD sensing both the pacing pulse and the resulting ventricular depolarization, i.e. double counting. This would be most likely to occur if one were to use A-V sequential or unipolar pacing modes. Thus, at higher ventricular pacing rates both the rate and PDF criteria could be satisfied. For these reasons we have avoided both unipolar and A-V sequential pacing in IACD patients, and required all pacemakers to be the ventricular bipolar type. Furthermore, we attempt to physically separate the IACD and the pacemaker leads as much as possible, e.g. placing one system in the RV endocardium and the other as a LV intramural lead system; in addition, recordings are also made to document the exact voltages resulting through the IACD lead.

FUTURE TRENDS

One can easily envision several desirable additions to the present IACD. These would include such things as non-invasive programming for all functions, some form of recording system to document events out-of-hospital and the ability to provide demand cardiac pacing. All of these features are distinctly possible. However, despite the apparent desirability, we must not let this device become so sophisticated that application to patients who could benefit is limited by the complexity of design.

The present IACD still requires some form of thoracotomy to position the LV apex electrode. If single catheter defibrillation could be accomplished as originally proposed,[1] transvenous insertion would greatly simplify device placement. Recently, single catheter cardioversion of VT has been re-evaluated and again shown to be effective.[6] However, any

device which is used for cardioversion of VT must also be capable of converting VF which may occur spontaneously or as a result of attempted conversion of VT. In either case, the energy requirements will increase and may exceed feasible limits of current designs. However, a single catheter IACD would still appear to be a distinct possibility with design modifications and appropriate determination of energy requirements.

SUMMARY

The present experience with the older IAD and the newer ISCD has documented that automatic conversion of life-threatening ventricular tachyarrhythmias can be effectively and safely accomplished. The newer IACD appears to offer several advantages over the older model but accurate rate counting and R-wave synchronization are two new features which now permit effective therapy for a relatively wide range of VT rates while retaining the ability to convert VF. Future IACD design improvements seems desirable, feasible and appropriate as long as the complexity of technology does not preclude practical application to the very large group of patients known to be at risk.

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EVALUATION OF DEVICES FOR THE PREVENTION OF SUDDEN DEATH: STUDY DESIGN FOR SAFETY AND EFFICACY OF THE DEVICES

M. D. CHEITLIN

1. INTRODUCTION

The responsibility of the Circulatory Systems Devices Panel of the Federal Food and Drug Administration is to advise the commissioner on whether the proposed device has been shown, in both in vitro and in vivo testing, to be both reasonably safe and reasonably effective. When a new device such as that proposed to detect potentially fatal arrhythmias and prevent sudden death is developed, there are few precedents available to provide a plan for its evaluation. However, previous devices such as the numerous pacemakers already tested, approved, and in use, give some help in developing plans for the evaluation. Certain aspects of the evaluation, such as material bio-compatibility, fluid tightness of the device container, mechanical flexion characteristics of leads, etc., have already been evaluated when the same materials and configuration were used for devices already tested and approved. Once tested, these components need not be retested to the same extent as was necessary originally.

The evaluation of a new implantable device to detect and correct potentially fatal arrhythmias must conceptually include the following steps:

2. IS THE DEVICE REASONABLY SAFE?

Materials Testing

Will the materials from which the defibrillator is made survive in the environment of the body (heat, pH, flexion stresses, shock)?

Is the defibrillator can fluid tight?

Are there interactions between materials and body fluids which are injurious? Is there device-tissue interaction such as allergy and toxicity?

Materials testing must be both with and without electrical activation.

3. IS THE DEVICE SAFE DURING ITS FUNCTION?

Arrhythmia Detection

Are there problems with the recognition of arrhythmias which would endanger the patient through falsely identifying benign rhythms as potentially fatal? If so, does this pose a danger to the patient if the device responds inappropriately?

Are there interfering signals which can cause false identification of fatal arrhythmias?

Can other programmers interfere with these devices?

Arrhythmia Correction

Are the energies delivered enough to cause myocardial damage or injury to the conduction system?

Are there dangers in converting an arrhythmia into a more serious arrhythmia, for instance, supraventricular tachycardia with abberation to ventricular fibrillation?

Does the device have a pacing function which will allow escape pacing if after defibrillation there is no spontaneous pacemaker which takes over?

3. IS THE DEVICE REASONABLY EFFECTIVE IN ACCOMPLISHING ITS PURPOSE?

Arrhythmia Detection

What are the rates of failure to detect ventricular tachycardia and ventricular fibrillation?

What are the rates of identification of benign rhythms falsely as ventricular fibrillation and tachycardia?

In other words, is the logic for arrhythmia detection sufficiently sensitive to identify all potentially fatal ventricular tachycardia and ventricular fibrillation and sufficiently specific to not mistakenly identify nonfatal arrhythmias such as supraventricular tachycardia or atrial fibrillation with abberation as a fatal arrhythmia?

Arrhythmia Correction

If the device can detect the arrhythmias in question, does it respond appropriately, either by burst pacing or defibrillation?

Is the lead system appropriate for delivering the lowest effective defibrillating discharge?

What is the lowest effective energy level for defibrillation?

What is the failure rate of the first defibrillation?

What is the shortest recycling length and sampling period until a second discharge can be applied?

What is the failure rate of the second discharge?

What should be the next step? A higher energy defibrillation? If so, how much higher should the energy be?

How many defibrillations should be attempted after the previous one was unsuccessful?

4. EVENTUAL PROGNOSIS OF THE PATIENT

What is the life span of the battery pack?

What is the component failure rate in patient use?

What is(are) the complication(s) in actual patient use?

a. Lead failure and displacement rate.
b. Complications of implantation.
c. Infection rate.
d. Defibrillator erosion.
e. Other component failure.

What is the mortality rate and what are the causes of death in whom the device is employed? In those patients where the defibrillator is explanted, does it still function appropriately?

5. PATIENT SELECTION.

What are the indications for the implantation of this device and what are the contraindications?

The problems of material durability and tissue compatibility can be attacked, for the most part, by in vitro and animal in vivo testing and by the use of materials and manufacture design with which we already have a wealth of experience from the development of pacemakers. There is no point in repeating work already done on materials and techniques used successfully in the same way for the same purpose and under the same conditions in pacemakers. A caviat here is that in order to transfer this knowledge, the materials must be subject to the same stresses, mechanical, chemical and electrical, that the materials are subject to in the conventional pacemaker. For instance, the increased energy discharges used in the internal defibrillator are markedly different from those delivered in the conventional pacemaker. Therefore, the durability of these materials, the effect on tissue under these different conditions, must be evaluated in vitro and in animal experiments.

Furthermore, in the IDE (investigational device exemption) and PMA (premarket application stage) stages, even after approval and release of these new devices, any devices that are retrieved from patients either through removal of the device because of failure to function or through

death of the patient, should be evaluated in the laboratory to check function and state of the device for evidence of material changes and failures. The report of these investigations to the F.D.A. is essential.

In the clinical trial of these devices, the following points must be considered:

1. Selection of patients for enrollment in this trial should take into account the fact that this is a new device with a potential capability of causing serious problems or death if it malfunctions. Only patients who have demonstrated the fact that they are high risk for developing potentially fatal ventricular tachycardias, who have failed to be suppressed by any arrhythmic agents after electrophysiologic testing, should be included. Patients who have had at least one documented arrest with ventricular tachycardia or ventricular fibrillation, who have had antiarrhythmic therapy chosen after EPS stimulation and have at least one breakthrough, should be considered. Also, those patients after an "aborted sudden death" where on EPS study no antiarrhythmic agents can be found to prevent the induced ventricular tachycardia and ventricular fibrillation could be considered since they have such a high potential for repeat sudden death.
2. In devices programmed to detect ventricular tachycardia and ventricular fibrillation by electrical criteria and rate criteria, without having an input from functional cardiac state, the patients should be tested in the electrophysiological laboratory to demonstrate whether the criteria could be falsely satisfied by the induction of tachycardia and rate dependent bundle branch block.
3. At the time of implantation of the device, it is desirable to induce the arrhythmia in the laboratory and to prove that the device performs appropriately to detect the arrhythmia and to successfully defibrillate or pace as indicated.
4. The logic built into the device to detect ventricular tachycardia and ventricular fibrillation, and after defibrillation, asystole with severe bradycardia, must be evaluated after implantation during the patient's normal activities. To do this, the patient must be monitored in such a way that all episodes, even those which would be self-limited and not clinically apparent, would be detected and appropriately responded to. This could be done either by telemetry or by ambulatory electrocardiographic monitoring for some time after

implantation. This should be done in every IDE and PMA patient. This monitoring should be done when the patient is engaged in activities which are normal for him, such as walking, sleeping, working, doing exercise, etc. The number of hours monitored may be 24, 48 or 72 hours or longer. After this arbitrary period, evaluation should be continued over a prolonged period reporting every clinical event with witnesses' reports and its outcome. Any interim hospitalization should be reported.

Since there will usually be no recording of these events by ECG when they occur, strict criteria for accepting an event as having been successfully detected and terminated should be established. Such evidence could be electrocardiographic, occurring while monitored or with ambulatory ECG, or a witnessed syncopal episode of the type experienced by the patient for which the device was implanted, successfully terminated in the short time which would be expected if the device had terminated the arrhythmia. All episodes should be recorded and reported.

Evidence of a syncopal episode successfully terminated could be interpreted in three ways:

1. That the device functioned appropriately.
2. That the device initiated the arrhythmia.
3. That it responded inappropriately to arrhythmias or events which were not ventricular fibrillation or ventricular tachycardia. For this reason, the course of a patient, number and duration of events should not be worse or more frequent after implantation than before. If the frequency of events increases after implantation then the patient should be rehospitalized for another period of controlled monitoring to help clarify what is happening.
4. The initial group of patients should be followed periodically with all complications recorded with periods of ambulatory monitoring reported to the F.D.A. After PMA approval, all complications and failures of devices should be reported to the F.D.A. All explanted devices should be recovered and tested and all those that come from the original and expanded group from the P.M.A. should be reported.

Because this is a new device all complications should be reported to the company and the summary report should be made to the F.D.A. for at least the first 2-3 years.

5. Periodic reevaluation of the patient should be done to test the

function of the device non-invasively. This testing should be at rest and with exercise. Various parameters of function of the device can be tested non-invasively such as its sensing capabilities, threshold, some test of battery life, etc.

6. Eventually indications for this device could be expanded. Patients with poor prognosis because of their underlying disease, for instance, coronary disease or cardiomyopathy with poor ventricular function might be candidates for this device if they otherwise qualified by having an arrhythmic breakthrough in spite of good medical management. Although death may occur due to the underlying disease which could not be avoided by even a properly functioning device, still the potential for testing the function of the device in detecting and responding appropriately to fatal arrhythmias is present, and even though the patient may die of the underlying disease, survival is not the only end-point being evaluated.

Finally, since we are dealing with a new and potentially dangerous device where the evaluation to prove safety and efficacy is so complicated, I believe that the principal investigators chosen to evaluate the device in the IDE and PMA stage should be recognized electrophysiologists capable of doing complete electrophysiologic evaluations prior to, during, and after implantation of the device. During the PMA evaluations, physicians who are not capable of performing these sophisticated electrophysiologic stimulation studies should not be investigators.

Obviously, once safety and efficacy are demonstrated and the appropriate clinical situations and circumstances defined where the device is beneficial, then the device may be implanted by cardiologists who are not necessarily electrophysiologists.

This is an exciting development in technology which promises an advance in preventing sudden death not previously achievable. A careful evaluation to define the indications and contraindications to the device's use and to minimize those situations where the device is ineffective or dangerous will help to establish the proper place of this device most rapidly and certainly in the treatment of fatal arrhythmias.

NEW DEVICE APPROVAL BY THE FOOD AND DRUG ADMINISTRATION

Dönald F. Dahms, MSEE, Scientific Reviewer,
Division of Cardiovascular Devices
Office of Medical Devices
National Center for Devices and
Radiological Health
U.S. Food and Drug Administration
Department of Health and Human Services

THE FOOD AND DRUG ACT

The first Food and Drug Act was signed by Theodore Roosevelt in 1906 after attempts at passage over several years. The book "The Jungle" by Upton Sinclair which revealed dangerous doctoring of meat and the addition of rats and other filth to the American food supply, coupled with an attendant drop in the sale of meat, finally led to its passage.

Thirty years later a chemist in Bristol, Tennessee, after much searching, found something which would dissolve the then popular sulfa drugs into a liquid form, namely ethylene glycol or "anti-freeze". After this "elixir" killed 107 people and President Franklin Roosevelt publicized an emotional letter from a dead young child's mother, the Food, Drug, and Cosmetic Act of 1938 was passed. This Act provided that drugs should be safe if used according to directions. The law extended coverage to devices and cosmetics. The cosmetics were included because a coal tar dye for lashes called "Lash Lure" had blinded and killed women in the early 1930's.

In 1962 after the thalidomide tragedies, the Kefauver-Harris Drug Amendments added the requirements for test data to prove the effectiveness of drugs. Effective May 29, 1976, the Medical Device Amendments were added to the law (H.R.1124). The Amendments define a medical device and are designed to reasonably assure the safety and effectiveness of all marketed medical devices. They presume interstate commerce in any device commercialization and supercede all less restrictive local laws.

The law now provides for:

- registration of all manufacturers, distributors or repackagers (not retail pharmacies or licensed practicioners in the course of their practice) and a listing of their marketed devices;
- restricted sale of certain devices by prescription;
- banning of devices that present an unreasonable risk or substantial deception.
- good manufacturing practices (GMP's) which require quality control procedures, record keeping and factory inspection;
- notification of all health professionals when a device presents an unreasonable risk of substantial harm to the public (possible repair, replacement or refund is provided; also, health professionals may be required to notify individuals who were treated with the device);
- custom devices which may be excluded from certain requirements of the law;
- non-financial technical assistance to small manufacturers; and
- premarketing approval.

The law requires certain approvals to be obtained or determinations to be made prior to the introduction of a device into interstate commerce. These are premarket notification (510(k)) and premarket approval (PMA). Before discussing these, it is necessary to describe the classification of devices and define safety and effectiveness.

The Amendments require all pre-Amendment devices to be classified into one of three regulatory categories and for the FDA to solicit the advice of advisory committees consisting of non-FDA medical and scientific experts in this classification.

The categories are:

Class I - Devices which pose little or no potential risk to health, and safety and effectiveness are assured by general controls (manufacturer registration, device listing and good manufacturing practices) example: manual stethoscope.

Class II - For devices where general controls are inadequate, performance standards must be established to assure reasonable safety and effectiveness - example: ECG monitors.

Class III - Devices which may cause unreasonable risk or injury to health and/or are life-supporting, life-sustaining or implants - example: cardiac pacemaker.

Cardiovascular device classification was completed and published on February 5, 1980 in the FEDERAL REGISTER.

SAFETY AND EFFECTIVENESS

The approval of a device will be based on the showing that there is reasonable assurance that it is safe and effective when used in accordance with its labeling.

Safety and effectiveness are determined:

- with respect to the persons for whose use the device is represented or intended,
- with respect to conditions of use prescribed, recommended, or suggested in its labeling, and
- weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.

Safety means, for example, no dangerous or morbid side effects, no toxic materials, and, especially in the case of life-supporting or life-sustaining devices, reliability. Safety must

be proven by, e.g.:

- the results of durability and environmental testing,
- reliability prediction,
- conformance to GMP's,
- field history,
- animal tests, and
- clinical tests.

Effectiveness means the device will have the effect it purports or is represented to have under the conditions of use prescribed, and is proven by:

1) well controlled investigations, including clinical investigations when appropriate, by experts qualified by training and experience to evaluate the effectiveness and/or
2) sufficient valid scientific evidence from which the effectiveness can be concluded by qualified experts.

INVESTIGATIONAL DEVICE EXEMPTION (IDE)

Clinical trials may be desired for products to be developed in the distant future or required for specific devices to prove reasonable safety and effectiveness for (510(k)s) or premarket approval applications (PMAA). In order to conduct such experiments or device trials on human subjects, an IDE must be obtained.

The IDE regulation has been in effect since July 16, 1980. It was mandated by the law (article 520g) and is described in the Code of Federal Regulations (21 CFR, Part 812). It refers to Informed Consent (21 CFR, Part 50) and Institutional Review Boards (IRB) (21 CFR Part 56) in its text.

In order to conduct a clinical trial, certain provisions of the Act must be suspended. The IDE section of the law permits this suspension of other sections such as labeling, registration, 510(k), PMA, and

GMPs. It applies to all devices except:

- pre-Amendment devices and those determined to be substantially equivalent to them by FDA (if used in accordance with the past labeling and not in an experimental manner - expires when PMA applications are mandated - see below)
- diagnostic devices,
- veterinary devices,
- custom devices (except those intended for commercial distribution.)

A distinction is made between significant risk and nonsignificant risk devices. A significant risk device requires application to FDA and formal approval, IRB approval, IDE labeling, informed consent, monitoring, record keeping and reports. The nonsignificant risk devices require all of the above except the FDA application and approval are replaced by an explanation to the IRB as to why the device presents no significant risk.

Sponsors of significant risk devices may apply to FDA before or after receiving IRB approval. FDA will respond within 30 days or the investigation is automatically approved. FDA requires the following preparation for an IDE:

- reports of prior investigations,
- an investigational plan,
- selection of qualified investigators (who must sign an agreement to comply with the IDE),
- IRB approval based on the report of prior investigations and the investigational plan.

Contents of the application are detailed in the regulation. At present for the clinical investigation of pacemakers, FDA concentrates on the in vitro testing and the results of other prior investigations. The judgements concerning the indications, contraindications, clinical protocols, adequacy of informed consent, and the evaluation of the benefits and knowledge to be gained versus the risk reside primarily with the IRBs. Some of the clinical concerns are obviated by the fact that there is close monitoring of each patient by the investigator who is expected to obtain informed consent and to report all unanticipated

adverse effects to the sponsor and the IRB. What is desired is a well controlled study exposing as few people as possible to a well designed and tested investigational product. FDA has placed certain limits on the clinical investigation of pacemakers. For example, pacemakers for general use are limited to five hundred maximum at first and then the number is increased in a stepwise manner until final approvals are rendered. At present, to apply for premarket approval (PMA), one hundred pacemakers must be followed for four months by experienced investigators. It is believed that a limited number of investigators with substantial experience with a device makes a better study. Intercommunication between investigators is desirable and should be encouraged by the sponsor. Follow-up of pacemakers is expected at one month, three months, six months and then every six months thereafter until completion of the study. True emergency uses of an investigational device is provided. Commercialization and test marketing is prohibited.

There are highly specialized or limited use devices which may never be marketed and may always be investigational. Some devices may be for research only and not bound for a premarket approval. As in any investigation, the applicant should specify the limits of the tests (the numbers of patients and centers) and the test plan. Of course, informed consent and record keeping are always required.

The sponsor is the principal interface with the FDA. It is the sponsor's responsibility to monitor the investigation, report all adverse effects, and terminate the study if an unreasonable risk develops. The sponsor must not prolong a study beyond its useful duration. In addition to the responsibilities discussed above, the sponsors, IRB's and investigators are responsible for certain record keeping and reporting, and they must permit FDA inspections.

PREMARKET NOTIFICATION (510(k))

A producer wishing to market a device which is substantially equivalent to a pre-Amendments device must notify the FDA ninety days prior to the intended date of marketing. This applies to:

- a new and unique device;
- a device new to a particular manufacturer; or
- a device modified with respect to design, manufacturing, materials, energy source, or intended use.

If substantial equivalence is determined, the device may be marketed. If not, the device must receive premarket approval if it is a class III device, or be able to be classified into class I or II. In some cases a petition for reclassification from class III into class I or II is appropriate.

Substantial equivalence was discussed in the "Report by the Committee on Interstate and Foreign Commerce" which accompanied the Medical Device Amendments. As stated there, the term "substantially equivalent" is not intended to be so narrow as to refer to devices that are identical to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. It should, however, be construed narrowly enough to assure reasonable safety and effectiveness.

The contents of the submission of a premarket notification is described in the 21 CFR, Part 807, Subpart E.

Eventually, all class III devices, including all pre-Amendment and equivalent devices still on the market, must receive premarket approval Thirty months after classification, or ninety days after publication in the FEDERAL REGISTER of a regulation requiring the submission of a PMA, whichever is if later, the application must be submitted to FDA. The thirty months is over for cardiovascular devices, but FDA has not published any regulations requiring the submission of PMAs for pre-Amendment cardiovascular devices.

PREMARKET APPROVAL (PMA)

Class III devices which are not substantially equivalent to pre-Amendment devices must receive premarket approval before they can be legally marketed in this country. Any such device which is marketed without approval is considered adulterated.

The mechanics of approval are as follows. Application is made to FDA following the format in the Department of Health and Human Services publication of November 1980 entitled "Guidelines for the Arrangement and Content of a Premarket Approval Application". One of the application requirements is a Summary of Safety and Effectiveness, which must include a description of the product and its uses and a summary of all in vitro, in vivo and clinical testing. When the application is acceptable, it is filed by FDA and action is required within 180 days of the filing date. Actual review is started soon after the filing date. FDA's advisory committee for cardiovascular devices, the Circulatory System Devices Panel, reviews the PMA and makes its recommendations to FDA.

Within eight weeks of the Panel meeting, an approvable or non-approvable letter is sent to the applicant. An approvable letter is sent following an acceptable review by FDA. The approvable letter describes any additional information that the applicant must provide to correct any minor deficiencies.

When the deficiencies are corrected, a final review process begins including review in the Office of General Counsel and the Office of the Associate Commissioner for Compliance. An approval letter announces FDA's final decision and a notice is published in the FEDERAL REGISTER. The Summary of Safety and Effectiveness and the labeling are then made available for public review. Challenges to an approval must be made within thirty days of the FEDERAL REGISTER Notice announcing FDA's decision.

A non-approvable letter will follow if FDA finds:

- a lack of showing of reasonable assurance of safety and effectiveness,
- labeling which is false or misleading.

The letter will describe steps required to correct such problems (including further research and testing) and indicate the appeal procedure, which must start within thirty days.

The premarket approval may be withdrawn, after due notice to the applicant and with an opportunity for an informal hearing, if FDA finds:

- the device is unsafe or ineffective when used according to its labeling,
- there was an untrue statement of a material fact,
- there is a failure to maintain records or permit access to them, and/or
- that new information shows a lack of good manufacturing practices, or the labeling is false or misleading.

Questions on this material or guidance on the approval process for cardiovascular devices may be directed to the author by phone at (301) 427-7559 or by mail at the National Center for Devices and Radiological Health, Office of Medical Devices, HFK-450, 8757 Georgia Avenue, Silver Spring, MD 20910.

NEW DEVICES: PACEMAKERS IN THE TREATMENT OF ARRHYTHMIAS AND PREVENTION OF SUDDEN CARDIAC DEATH

Dr. Mirowski: Development of a useful and effective antiarrhythmic drug is not a simple matter. With regard to an implantable "antiarrhythmic" device, the task is more complex because in addition to the usual requirements of safety, efficacy, and reliability, a permanently implanted device must have a number of functional and structural attributes difficult to implement. I don't want to go into the entire developmental process that we have gone through, but would like to center on one very important aspect. We now have a clearly useful clinical device characterized first by defibrillating capabilities, and secondly by cardioverting capabilities. This means that it can identify and treat the entire range of ventricular tachyarrhythmics with an R wave synchronized discharge. This combination of cardioverting and defibrillating capabilities is very important, but we understood from the early days of our work that the defibrillating capability is the prerequisite for further developmental efforts. This has already been alluded indirectly by several of the speakers yesterday and today,in that electrical stimulation of the heart and electrical treatment of ventricular tachycardia frequently results in acceleration of the rhythm to a much more serious tachycardia or even to ventricular fibrillation. When we began our clinical studies approximately 3 years ago, the device had defibrillating capabilities, but we have expanded the therapeutic potential of the device to treat ventricular tachycardias. It is one thing to experiment or treat patients in an electrophysiology lab with pacing or catheter stimulation or in a coronary care unit and another thing to send this patient outside the hospital with an implantable device. I think it would be highly undesirable to do the latter unless there was a mechanism to deal with acceleration of arrhythmias, the

device that we are using has such capability: in case of acceleration it recycles, identifies the new arrhythmia and terminates it. We have seen 2 patients in which this occurred 3 times with an entirely satisfactory result. In order to further increase the safety margin of the device, we have added R wave synchronization to the recent model, placing the discharge outside the vulnerable period of the cardiac cycle.

I would like to take exception to Dr. Winkle's reference and this refers to what he called the general early enthusiasm. I don't know what his time frame is, but our work was initiated 15 years ago and thus is not early enthusiasm. We built and successfully tested successfully the first experimental prototype of our device in 1969. Yet our group is virtually alone in this uncharted area, as can be seen from this symposium in new drugs and devices. The automatic implantable defibrillator doesn't appear on the program. I certainly interpret this not as a criticism, but as a kind of skepticism, a very important quality of physicians, and I certainly wouldn't call this an early enthusiasm.

I have been asked why we abandoned our initial electrode system. At first in the late 60's and early 70's, we used a single catheter system comprised of two electrodes, one distally and one located more proximal and this system was very effective. The distal electrode was wedged in the right ventricular apex, while the approximate electrode was located at the level of the superior vena cava. I was somewhat surprised that Dr. Prystowsky, in his presentation gave credit for this electrode configuration to Drs. Kellogg and Zipes. We abandoned this system because in spite of its effectiveness, we noted, marked variability of the defibrillation threshold. We were occasionally able to defibrillate to 5 joules, even at times with only 0.5 joule. But then in the same animal, under different circumstances, we required 40 or 50 joules. We explained this as variability in electrode

position and we decided to go on to clinical trials, where we decided to temporarily use a system with one catheter electrode located in the superior vena cava, but the other electrode a patch affixed to the cardiac apex.

Dr. Cheitlin: I would like to ask Dr. Mirowski whether there are plans to put a memory loop in the defibrillator so that we can find out what the rhythm was before and after the defibrillation.

Dr. Mirowski: I think that this is an extremely important element of any implantable device. Work is underway and I hope that in the not too distant future, the device will have this capability.

Dr. Reid: Dr. Mirowski discussed starting out by trying to treat ventricular fibrillation. I learned in school that ventricular fibrillation was the primary problem in the community. However, those of us who have had a chance to observe patients during electrophysiological testing, or have seen Holter monitors of out-of-hospital cardiac arrests, recognize that in fact ventricular tachycardia is the initial killer and ventricular fibrillation is subsequent. That is at least my perception of the problem - so we have had it reversed for many years. This is particularly true if one begins to treat these tachyarrhythmias with drugs, so that the implantable defibrillator is appropriately aimed at both ventricular tachycardia and ventricular fibrillation, ventricular tachycardia first and ventricular fibrillation later, is really the usual natural history in my view. It certainly would be nice to have a device capable of having not only memory, which could telemetered, but with pacing capabilities as well.

Dr. Engel: I would like to continue some of the skepticism that Dr. Mirowski alluded to previously by asking members of the panel - I know Dr. Griffin has some thoughts on this about how efficacy should be evaluated in devices such as we have discussed. One usually thinks in terms of double-blind placebo ,

controled, observations as best. How does one evaluate a life-saving device such as this?

Dr. Griffin: I think that is an important consideration, Toby and I am not sure that it is a consideration that we have an absolute answer to. I think the data that Phil presented this morning, estimating the impact of the implantable defibrillator on survival, is one way to go about it. Unfortunately this involves assumptions and always leaves some question as to the final conclusion. However at this point in time one simply can't randomize patients to placebo defibrillators or placebo implantable devices. One just has to make sure that the assumptions one makes in estimating survival are are as accurate and as fair as possible.

I think that when comparing devices to estimate their relative efficacy, there are two very important factors to consider. One is to compare equivalent patient groups. Obviously the patient that has ventricular flutter, or sudden death from ventricular fibrillation, is a considerably different patient from one who has sustained ventricular tachycardia at a rate of 150 with hemodynamic competence. What is effective for the latter may be totally inappropriate or ineffective for the other. Secondly, I think you have to be very careful in evaluating data from these patients when comparing automatic versus non-automatic systems. Most of the comments we have heard refer specifically to automatic devices but in my own experience and in the experience of some in the audience, particularly Jeremy Ruskin, non-automatic patient-activated or physician-activated devices can be very effective in patients with ventricular tachycardia and very safe. In assessing the impact of these systems, I hope that I've not underplayed the role of pacing and there is certainly a role for non-automatic devices in large segments of the population with recurrent ventricular arrhythmia.

Dr. Cheitlin: I would like to know whether there are plans to have several models of response, one perhaps for ventricular tachycardia and one for ventricular fibrillation. It is obvious that the low energies used to convert ventricular tachycardia would not necessarily incapacitate the individual, and the person wouldn't necessarily fall down. It might be possible to be able to identify and respond differently to these two arrhythmias.

Dr. Mirowski: I am in full agreement with Dr. Cheitlin and am sure that technological development will solve this problem satisfactorily.

Dr. Engle: If not, I wonder if some of the panelists would comment in some detail on contraindications to use of this device. I am thinking of general medical and social contraindications.

Dr. Gallagher: I want to ask a question which relates to that issue. I wonder if Michel or Phil have any information about the effectiveness or of the energy requirements of the device in the setting of active ischemia. Ronnie Campbell alluded yesterday to the arm of sudden death which is mediated by on-going ischemia. I wonder if we might not learn something about the natural history of sudden arrest by observing the frequency with which the device fails to defibrillate. Would we expect from your animal work, that with active ischemia the device to be able to defibrillate? Otherwise the device wouldn't be applicable for implantation in patients in whom coronary spasm is thought to be present and in whom Prinzmetal's angina was the mediator of the of fibrillation.

Dr. Reid: We have not known of any patients automatically defibrillated in whom there was subsequently shown to have been an acute myocardial infarction. We have, however, implanted the device in one patient who had a history of documented coronary spasm and her defibrillation thresholds, which were looked at in the operating room, did not appear to be excessively high,

but I don't think that specifically addresses the question John has asked. Experimentally the ventricular fibrillation threshold might be quite different depending on the acuteness and the degree and extent of the ischemia. We will merely have to wait to find if that is true clinically or not. The number of out-of-hospital defibrillations that we have seen, underscores the data of many others here, who have pointed out that the majority of patients, when they do arrest, they do not have myocardial infarction. You asked, Toby of the contraindications to the defibrillator. I am sure that many could name more than I, but certainly one contraindication for us is the patient who has incessant ventricular tachycardia, who is not a candidate for this particular device. The device will shock the patient effectively, but if we have not done something to control the rhythm, the design of the device limited to 100 discharges, will require you to have to replace the unit. Certainly, therefore, incessant ventricular tachycardia is one contraindication. Another contraindication that is very difficult to assess is the patient who is either mentally incapable of deciding for himself that this should be done or has a disease process precluding survival over an extended period of time, which we have arbitrarily set at one year.

Mr. Rahmoeller: I thought it appropriate to make some comments about the labeling. I would rather refer to the labeling as information provided to the physician, because I would like it looked at as not just a legal requirement. If you can define a patient population in whom there is a clea benefit to risk ratio in providing the device, then it is relatively easy t get the device to the market. That certainly happened with PTCA with the first two catheters that were provided. One approach is to define a patient population in whom the benefits clearly outweigh the risks, get it to the market using those indications and then broaden the indications as one learn

more and more of the device, rather than trying to piggy-back everything and make the device all things to all people the first time through. Often the manufacturers don't offer information in the physicians manuals that provides the physicians buying the device the thought processes that the investigators have gone through in defining those patients in whom the device should be used. I think providing such information in the physician's manuals will prevent or at least inhibit the misuse of the device, helps to get the device to the market faster, and allow its use to be expanded in a step-wise fashion.

Dr. Altman: We heard have today about the multi-faceted aspects of the anti-tachycardia devices. How many people on the panel actually include biomedical engineers on their staff and if so, in what capacity do they operate on a daily basis?

Dr. Gallagher: We have one, and I think everybody up here has one. Our biomedical engineer fixes our devices and makes in-house devices for our own use. I expect that is how most of the panel employ biomedical engineers.

Dr.Reid: We at Hopkins also work fairly extensively with engineers and physicists. Most are not located within the hospital itself, but we have a heavy dependency and interchange with those in the basic electrical sciences relating to the defibrillator.

Dr. Dahm: Pacemakers are rather complex devices, the new pacemakers that are dual chamber physiological are very complex, and I believe, that the medical profession should have engineers on their staff to make certain measurements and to do certain evaluations on pacemakers. As a matter of fact, Montifiore Hospital has two very good engineers who actually work in the operating room, and make measurements of stimulation thresholds and what not.

Dr. Griffin: We take a slightly different approach. We employ a biomedical engineer, but his functions largely concern research devices. For clinical

work, we employ cardiovascular nurse specialists whose total orientation and function is their work either in the implant area, with the accumulation and collection of data at the point of implantation, or in pacemaker follow-up. We don't employ biomedical engineers for clinical care of patients with implantable devices but instead use cardiovascular nurse specialists.

Dr. Winkle: I think that as we move into devices to treat ventricular tachycardia, we can't really have our cake and eat it too. I notice that there have been a lot of comments from the regulatory side concerning their interest in how often the device shocks supraventricular tachycardia with aberration or sinus tachycardia with bundle branch block. I think even a lot of experienced electrophysiologists, who are telling the world that you can't tell these rhythms from ventricular tachycardia without 5 catheters and a 4 hour procedure, sort of drop their jaw when one says that the implanted defibrillator is going to shock these rhythms. The reality is the trade off that if you want to avoid shocking some of these rhythms, you are going to not shock some of the rhythms that you would like to shock. I think people are going to have to accept the fact that you may occasionally be shocking patients for other than the rhythm that the device was put in, and the question is how safe that is? How uncomfortable to the patient? I think that is just a principle everyone, including the regulatory agency, needs to keep in mind.

I would like to ask Eric and Michel, who have had experience with catheter defibrillation, to describe the tissue damage that occurs, not when giving low energy shocks, but 15,20,or 30 joules through the catheter.

Dr. Prystowsky: We don't have information about tissue damage in man because of the two patients in whom we used it in, one family refused autopsy and the other patient lived. I do know though that Dr. Kline has looked at this in some patients who have died and that there has been no tissue damage. I am

told that in the dog lab experience with repeated shocks over periods of time, with high energy levels, there has been no damage in any of the dogs when this has been looked for. We don't have experience at the Krannert regarding this, but there are at least two other institutions that have had such experience and have not seen damage from high levels. I would expect there would not be damage from the low levels of energy we use.

Dr. Mirowski: Our experience has been published, and the data are very encouraging. The damage is minimal, usually limited to a few superficial hemorrhages. This includes human data because we used catheter defibrillation in 1972-73 during open heart surgery in 11 patients, and two (I think) died. The autopsy did not reveal any significant changes.

Dr. Prystowsky: I don't think we are dealing with either-or sorts of questions. The role of the transvenous cardioverter is two-fold. One is in an acute setting, unsuitable to surgical procedure. It is simply a transvenous device. The second is implantation, as with Dr. Mirowski's units, with cardioverter activity as well as back-up defibrillatory and pacemaker activity, the device that we will hopefully get to in the near future. The primary goal of the device is based on the philosophy, as Phil has mentioned and that we have all come to realize in the electrophysiology lab, that the onlogger of ventricular fibrillation in a great many patients is ventricular tachycardia. If we can get it to ventricular tachycardia with very low levels of energy as well tolerated by patients, I think this is one reasonable approach. I am by no means stating that this is the only approach, but just one approach that we happen to be advocating at the present time.

Dr. Ruffy: I have a comment regarding Dr. Gallagher's question. We have studied the influence of acute ischemia in dogs, regarding the feasibility of defibrillation with an electrode placed in the central ischemic region during

the very acute phase of coronary occlusion. This was published by biomedical instrumentation some time ago. We did not find the defibrillation threshold changed by the acute ischemic event. If there is spontaneous fibrillation and you defibrillate the heart, which you can do as easily as before the occlusion, then there may be a tendency to immediate refibrillation if the area of ischemia is large enough. The defibrillation threshold per se does not change and the capability of defibrillating is not modified. We have completed a series of experiments in conscious chronically instrumented animal and also don't find that there is a significant change in the capability of defibrillating the heart, even days following the occlusion thus, I think there is hope, in the sense that even during an acute ischemic episode the patient will be defibrillated, provided the infarct is not enormous.

Dr. Engel: I have a question of a regulatory or even of a philosophical nature, concerning contraindications for the device even when it may be effective. Are there certain requirements that ought to be written as to how the device is made available, such that certain patients will not receive this device even though it is effective. One might be making a trade off of sudden death for a slower, more painful death.

Dr. Cheitlin: Let me just say a word and then Glenn or Don may want to add my comment. My feeling about the F.D.A. is that it is not involved in telling doctors how to practice medicine. I think there is a responsibility that the profession has, that they must assume, and we certainly don't want government, through a committee or a regulatory agency, to start regulating that kind of decision. I think that would be something that we would resist. On the other hand, if the profession drops the ball on things like that, and patients begin to be hurt by doctors, certainly there is going to eventually be a requirement by the consumer that may force legislation to start having

governmental committees telling doctors how to practice medicine. If that happens, that is a big mistake, and it will result because the doctors have stopped being professional.

Mr. Rahmoeller: Mel is right, at least partially right.

Dr. Cheitlin: Only partially right with the F.D.A.

Mr. Rahmoeller: When we review an application, the burden of purpose is on the manufacturer, on the sponsor of the application, to show that the device is reasonably safe and effective for its intended use. At that point he has to show what the indications are, and show how, under those circumstances, the device will perform. Is it going to sense in - appropriately, is it going to cause some harm and to what extent will it cause some harm? What is the false positive/false negative rating and conversion or in-correct sensing? Once the device is on the market, it is up to the physician how to use it and I think Mel's comments are right. You can use the device however you want, once it is on the market. That is at your own risk, but you are not violating the Food and Drug Act by using a device the way you see fit, even though it may not be indicated for that use. What I am a little bit afraid of, from what I hear from the panel, is that a lot of revisions and modifications are going to be made to the device so that it may be all things to all people. By the time you get a device that defibrillates and paces and cardioverts, all in the same device, I think you will have a very difficult task in defining the patient populations and what the benefits and risks are. I think that at least it appears that there is probably a patient population in whom one can quite safely say that the benefits outweigh the risks. I think there is some benefit in trying to seek approval and get the device on the market for these uses, get some experiences with these uses, before one tries to go and make this a universal device and then run into some real problems.

Dr. Mirowski: I agree entirely. I think that further technological progress should not interfere with the availability of present devices for the population for which it is intended. I think progress will continue, and the device at a certain point should be presented for approval and evaluated and used by the populations for which it is intended.

Dr. Prystowsky: The points are extremely important and go beyond these new devices. For example, the so-called physiologic pacemaker devices, the DDD's now available, or any kind of AV sequential pacing, are devices that anyone and everyone in our community are putting in. Even though we say there are specific indications for them, once they are released, any doctor can use them in any particular way they want to. Many of the pacemakers have very complex firing structures, such that they will fire and not be malfunctioning and we are forever getting strips sent to us of patients who supposedly have malfunctioning pacemakers just because the physicians don't understand the way that the spikes go into the cardiogram. I think this is a general problem and I worry about this too with the new devices that we are working on, the anti-tachycardia and anti-fibrillatory devices. I don't know how to get around it, but certainly we have seen this problem in the last year with the newer pacemakers, and yet everybody is putting those in. I ask the F.D.A. members, if there should there be restrictions on newer pacemakers, - everybody is putting those in? Should there be restrictions, on even things like physiologic pacemakers, to people who have expertise in that area?

Mr. Rahmoeller: I didn't bring it up before, because I really think there are two different approaches to the investigation of the physiologic pacemakers and the anti-tachycardia devices. I think the anti-tachycardia devices have been investigated by a fairly small investigator groups, basically as research devices, trying to get information. I think that because of the way devices were handled at the time the law passed, in the

case of physiologic pacemakers, those haven't been handled the same way. I think that manufacturers tend to want to tell the world what they have coming down the line and the physicians don't generally look at the clinical investigation of those devices as providing much information. The reason I say that is that, in two PMA's that I have recently reviewed, the clinical data that was initially provided on those PMA's, (in one case covering about 600 pacemakers), in 12% of the cases there was no implant report provided to the sponsor. In an additional 22% of the cases, there was absolutely no follow-up information provided to the sponsor on pacemakers implanted for two months and longer. In a second study (involving about 300 pacemakers), in 33% of the cases, there was either no follow-up or it had been at least 5 months since the patient had last been seen, for pacemakers implanted for approximately 10 months or less. What we found from clinical investigations of pacemakers, is not much information telling us if the device should or shouldn't be marketed, but very important information about retrograde conduction, about cross-sensing between atrial and ventricular channels in the pacemaker, about polarization of electrodes that has an effect on refractory periods that are rate dependent. These things are very important and I think it is wrong to overlook these so I do want to emphasize the need to get this information.

Dr. Cheitlin: I would like to point out that all of the statements made are correct. They are all important. There is no question that once a device is released, that it can be misused and misused badly. My point is that that is not the business of the F.D.A., but the business of the medical profession and it has always been the business of the medical profession. We are talking about patients that doctors have always had to make decisions about: who to operate on, what medicines to use, when to use them, how frequently to use them, to recognize the side effects, to recognize the dangers. I think

the same thing is true with these instruments. I think the medical profession has a responsibility to police these things and to make available the information necessary for the physician to make a decision. If the medical profession falls down on it, somebody else will do it, but I think that would be a tragedy.

Dr. Engle: I would like to thank all of you gentlemen for your participation.

PHARMACOLOGIC PRINCIPLES IN THE USE OF NEW INOTROPIC AGENTS

JAY N. COHN, M.D.

In the syndrome of left ventricular failure depressed myocardial contractile force is an important mechanism of the impaired pump performance. In the traditional therapy of heart failure digitalis glycosides have been used in an effort to augment the depressed myocardial contractility, and diuretics have been employed to correct the abnormal sodium retention.

In recent years vasodilator drugs have been added to the regimen of patients who remain symptomatic because these drugs have been shown to produce a marked augmentation of left ventricular performance not by augmenting myocardial contractile force but by reducing the impedance to left ventricular ejection and thus allowing for improvement in left ventricular emptying (1). These drugs also often increase vascular compliance and thus result in a reduction in ventricular filling pressure (2).

Several observations over the past few years have made it apparent that a search for more effective inotropic agents for use in chronic congestive heart failure would be appropriate. First of all, careful follow-up of patients with congestive heart failure entered into drug trials in medical centers has revealed an astonishingly high mortality rate. In the first year after identification of patients who remain symptomatic from heart failure despite therapy with digitalis, diuretics and often vasodilator drugs, between 30 and 50% of the patients have died (3). By the end of two years as many as two-thirds of these patients have died. This experience suggests that present-day therapy for this advanced stage of heart failure is not very effective. Secondly, the use of digitalis as an inotropic drug for the treatment of heart failure in patients with normal sinus rhythm has increasingly come into question. In some countries the use of digitalis for this purpose has fallen into disfavor. In the United States its use continues in part because of tradition and in part because several carefully controlled trials have revealed evidence for some albeit slight efficacy (4).

Nonetheless, recent studies suggesting an adverse effect of digitalis on mortality rate in patients who have sustained an acute myocardial infarction have encouraged physicians who continue to use the drug to at least use it in low doses and have convinced all physicians that this drug is not a life saving agent in the treatment of chronic congestive heart failure.

Just as sodium nitroprusside has served as a gold standard for the development of oral vasodilator drugs, so has dobutamine served as a gold standard for the development of oral inotropic drugs. Although inotropic and vasodilator drugs have clearly distinct pharmacological actions, their effects on left ventricular function in patients with heart failure is so remarkably similar that distinction between these pharmacologic effects is often more difficult than it might otherwise seem. Infusion of nitroprusside and dobutamine in patients with severe heart failure result in similar increases in cardiac output, a similar reduction in pulmonary wedge pressure and similar falls in systemic vascular resistance and pulmonary vascular resistance (5). Even heart rate effects are not strikingly different. The major distinction between the response to these two diverse agents is their effect on arterial pressure. Nitroprusside results in a slight but consistent fall in both systolic and diastolic arterial pressure whereas dobutamine because of its positive inotropic effect tends to augment systolic pressure even though diastolic pressure remains unchanged. Thus these two agents both augment left ventricular performance with a shift upward and to the left of the Frank-Starling curve, but the inotropic drug accomplishes this improvement in pump function by augmenting contractile force and secondarily reducing systemic vascular resistance whereas the vasodilator drug primarily reduces systemic resistance and improvement in pump function follows (5).

Identifying an inotropic drug and distinguishing it from a vasodilator drug requires demonstrating that the agent increases the velocity of contractile element shortening or the rate of circumferential fiber shortening. An increase in the rate of left ventricular pressure development in the isovolumic phase of cardiac contraction is often taken as an index of increased contractile element shortening rate (6). Non-invasively some have used the velocity of left ventricular wall thickening measured by echocardiography as an index of fiber shortening rate (7). Presystolic measurements appear to be most appropriate to separate inotropic from vasodilator effects

since ejection indices are so profoundly affected by cardiac loading conditions that they are altered by arterial and venous dilator drugs. If one were designing an ideal inotropic drug one would choose an orally effective compound which increased contractility but not heart rate, which had no direct peripheral vascular effects so that it could be titrated purely for its myocardial properties, that exhibited no tachyphylaxis with chronic administration and was compatible with vasodilators, diuretics and digitalis. Furthermore, one might seek a compound which did not depend for its activity on beta receptor integrity because of the concern that beta receptor responsiveness may become down regulated with chronic administration and because of the concern that stimulation of beta receptors might also increase the risk of ventricular arrhythmias.

One of the earliest orally effective vasodilator agents which was studied in heart failure is one which probably has none of these ideal properties except for its oral effectiveness. Ephedrine is a sympathomimetic agent which not only acts through beta receptor agonism but also probably exerts its effect largely through endogenous release of catecholamines and is therefore dependent for its action on adequate stores of norepinephrine. Tachyphylaxis would be expected to chronic administration of this drug, and furthermore it has a peripheral vasoconstrictor effect which tends to counteract the pump function benefits of its inotropic effect. Nonetheless, single oral doses of 50 mg ephedrine can produce a prominent improvement in left ventricular function (8). Because of its vasoconstrictor effect, however, the augmentation of cardiac output in response to ephedrine may be associated with a further rise in pulmonary wedge pressure accompanied by a rise in arterial pressure. When ephedrine is combined with a vasodilator drug such as nitroprusside in order to reduce systemic vascular resistance, the effect of the combination is better than the effect of the nitroprusside or the ephedrine alone. Therefore it is clear that an inotropic agent when added to a vasodilator drug can produce a further augmentation of left ventricular performance.

A number of inotropic drugs which appear to operate through stimulation of $beta_1$ receptors have been tested (Table 1). Some of the orally effective drugs in this list are probably predominantly $beta_2$ agonists whose action is more prominent in the periphery than in the heart. Although these drugs may produce a cardiac stimulating effect by virtue of reflex response

to the peripheral vasodilator effect, it is likely that the beneficial hemodynamic effects reported to drugs such as salbutamol and pirbuterol represent at least in part the effect of concominant $beta_1$ receptor stimulation. Prenalterol and ICI-118,587 represent more selective $beta_1$ agonists which may be viewed as partial agonists associated with beta receptor blockers. These drugs also appear to augment left ventricular performance. Studies to date have not satisfactorily proved chronic efficacy of these beta agonists and indeed several of these drugs have been withdrawn from clinical testing because of suspected adverse effects. Since these agents work through an endogenous mechanism which is fairly well understood, approval of such an agent for chronic oral therapy would depend primarily upon evidence for chronic efficacy and lack of toxicity.

More provocative are inotropic drugs that do not appear to operate through stimulation of beta receptors. Digitalis, glucagon and aminophylline have been available for many years but their efficacy as inotropic drugs appears to be only modest. Newer agents appear to be considerably more potent but their mechanism of action remains uncertain. It is likely that these drugs work either by augmenting cytosol concentration of calcium within the myocyte or by increased senstivity of the contractile apparatus to calcium (9). Augmentation of calcium concentration probably results in large part from increased transmembrane transport. An understanding of the mechanism of action of these drugs is not necessarily a prerequisite to their approval and clinical use. However, since these drugs appear to act through a unique mechanism not normally utilized by the body for augmentation of contractility, it would seem that considerable evidence would need to be presented regarding their safety with long-term administration before they should be widely employed.

All of these non-adrenergic drugs appear to have both inotropic and vasodilator properties and the dose response relationship between these two actions would also need to be worked out. Amrinone, the first of this group of compounds to be subjected to clinical trial, AR-L115BS, MDL 17,043 and MDL 19,205 all appear to exert their inotropic effect even in the presence of propranolol. All these drugs also appear to augment myocardial cyclic AMP levels and all appear to have some inhibiting effect on phosphodiesterase. How much of their inotropic effect can be attributed to the phosphodiesterase inhibition is not known. Furthermore, since each of these drugs has unique

biochemical structures it is likely that they act through different mechanisms. It is of interest, however, that each of these drugs appears to produce more increase in contractility than in heart rate, thus raising the possibility that inotropic and chronotropic effects can be dissociated (10). All of these drugs also appear to have a rather sustained duration of action after oral administration and therefore possess at least favorable pharmacokinetics for chronic administration. Although the potency of these agents has not been directly compared, at least some of them appear to be equi-potent with infusion of dobutamine in doses as high as 15 μg/kg/min in patients with congestive heart failure.

The stage then is set for testing what is an important unanswered question in clinical pharmacology: Can a chronic increase in myocardial contractility be produced and is this augmentation of contractility associated with improvement symptomatology and/or improvement of life expectancy in patients with severe congestive heart failure. The problems of designing studies to test chronic efficacy of orally effective inotropic agents is complicated. Such complications also have plagued clinical trials of vasodilator drugs in a similar patient population. The problems relate not only to the vagaries of diagnostic criteria for congestive heart failure and our limited tools to assess severity, but also to the question of how to objectively evaluate the response to therapy and to whether mortality, exercise tolerance or quality of life should serve as the major end-point. Until such studies are carried out we must be cautious in extrapolating the dramatic acute improvement in hemodynamics which may be induced by these drugs to their chronic application. It is nontheless clear that chemicals which fulfill our criteria for the ideal inotropic drug can be synthesized. After trials of these agents have been conducted the place of these drugs in chronic therapy should become clearer.

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TABLE 1

Beta adrenergic inotropic drugs

1. Norepinephrine
2. Epinephrine
3. Isoproterenol
4. Dopamine
5. Dobutamine
6. Ephedrine
7. Salbutamol
8. Pirbuterol
9. Prenalterol
10. ICI 118,587

THE CLINICAL ASSESSMENT OF A INOTROPIC DRUGS:

Barrie Levitt, M.D., F.A.C.C.

Until a few years ago, the clinical assessment of new inotropic drugs was a matter of purely academic interest. The only effective inotropic drugs available for oral use were digitalis and its derivatives and for parenteral use a number of catecholamine derivatives whose brief duration of action mandated either continuous or intermittent intravenous administration. The assessment of inotropic drugs for long term use was largely limited to experience derived from the study of digitalis materials.

The experience with digitalis materials revealed that clinical and hemodynamic effects were most prominent in patients with heart failure. Hemodynamic changes were difficult to demonstrate in normal subjects in whom cardiovascular reflexes were felt to vitiate hemodynamic correlates or inotropic activity. Thus, clinical efficacy studies of digitalis materials were generally restricted to patients with heart failure.

This concept, rightly or wrongly, has been extrapolated to the assessment of inotropic agents in general. Recently, a number of inotropic agents effective when given by mouth have become available for study. The question of how to assess the clinical efficacy of these drugs suddenly became an urgent clinical pharmacological problem. There are two circumstances in which the drugs of this kind are used in man initially. First, there is the carefully controlled study usually undertaken at a university center with a large referral base of patients with significant heart failure. This type of center is equipped to assess efficacy of inotropic drug in the population in which it is meant to be used. Second, as soon as initial pharmacological or clinical reports concerning a new inotropic agent begin to appear, there is urgent demand from practicing physicians with patients in intractable heart failure to obtain the new agent on a compassionate or emergency basis. It is thus essential to organize the emergency use of such drugs in a manner that will maximize the amount of information to be derived concerning both their safety and their efficacy.

It seems appropriate to approach this problem by beginning with an attempt to maximize the information to be derived from the emergency use of a drug, since this is clearly the most common context of early use and the environment in which patients are most easily recruited. If meaningful data are to be obtained, it is important to require that patients be classified on the basis of certain strict entrance criteria. These entrance criteria should define their New York Heart Association functional classification (usually Class III or Class IV) and document the need for emergency treatment. Hemodynamic criteria, such as limits of cardiac index, or left ventricular filling pressure with which these patients present might be used to define eligibility for the emergency use of the drug.

Patients who are less symptomatic should undergo exercise testing. Limits of exercise capacity, both minimum and maximum, should be defined for patients in whom exercise tolerance will be a parameter to be measured. An important part of an emergency protocol is obtaining baseline measurements on approved alternative therapy. If this baseline period is sufficiently long that significant numbers of

measurements can be made, it may serve as a control period. These control periods may identify those patients who improve simply when they enter into a study. Patients who deteriorate on maximum alternative therapy are also identifiable. Depending on how the trial is organized, one might limit the emergency use of the drug only to those patients who get worse on alternative therapy or to those patients who remain stable and evaluate each subset of patients separately. However, it might be possible to define a subset of patients who are sufficiently controllable on the alternative regimen to make them suitable for inclusion in rigorous controlled trials.

In the most severely ill patients, attention should be directed to the establishment of an acute intravenous dose response relationships with respect to defined parameters of cardiac function. This permits initiation of needed treatment and provides documentation of drug effect on invasive parameters. This approach combines an exploration of the dose response relationship, with the optimization of infusion rate or dose, and injection frequency. It thus serves both the interest of the patient and of the

investigation. If a transfer of patients to oral therapy is anticipated, a switch from a continuous intravenous infusion regimen to intermittent intravenous administration is appropriate to attempt an assessment of the optimum frequency of drug administration. The repetition of hemodynamic measurements that were made at prior to therapy is important for proper patient management and in order to obtain data needed to establish drug efficacy.

In less ill patients, the initiation of oral therapy can be attempted as the first step. Measurement of invasive parameters of cardiac function is desirable. The exploration of dose related effects is an important objective. A properly planned study can lead to an optimization of dose and of frequency of drug administration, without compromising the clinical management of the patient.

Patients who have completed either the intravenous and/or the oral phase and have derived benefit from therapy can serve both themselves and the investigation by participating in a program or randomized withdrawal. On purely clinical grounds, a strong argument can be

made for a randomized withdrawal of the drug. If the patient has done well on the new drug, withdrawal is important to establish a continuing need for the drug. After therapy, some of the patients may be sufficiently compensated to function without continued inotropic support. In the setting where the patient can function well without the drug, and the drug's long term safety has not been established, withdrawal of the drug is genuinely in the patient's interest. On the other hand, withdrawal data can also serves to demonstrate efficacy. Randomized withdrawal is one form of controlled trial that might be used in establishing the effectiveness of a beneficial therapeutic intervention. On the other hand, if a patient has done poorly on therapy, withdrawal of the drug may help to determine whether the drug is still active or is contributing to the clinical deterioration. Thus, both in the setting of the patient doing well on drug and in the setting of the patient doing badly on drug, a clinical and investigatinal arguments can be made for drug withdrawal. This approach utilizes patients who had been in emergency programs to suggest drug efficacy.

In summary, there is considerable useful information to

be obtained from compassionate drug treatment programs. First, the demonstration of dose related effects on cardiac output or cardiac index is an attainable objective. In the short term, it can be assumed that spontaneous dose related augmentation of cardiac output or cardiac index does not occur by chance alone. Similarly, dose related decreases pulmonary capillary wedge pressure or pulmonary artery pressure may be demonstratable. These can also be assumed not to occur in the short term by chance alone. Such dose related changes in hemodynamic parameters can establish a drug effect. Thirdly, the time course of the hemodynamic effects of the drug can be defined. This information is important to optimize the frequency of drug administration in rigorous trials and in ultimate clinical use. Finally, during this kind of study the hemodynamic effects of a particular agent can be compared with other correlates of inotropic activity such as phonocardiographic systolic time intervals, echocardiographic parameters and changes in radionuclide ejection fraction. While these parameters may not be sufficiently sensitive for regulatory decision, they support the demonstration of an inotropic effect and may help in non-invasive studies

of efficacy. If possible, an attempt should be made to evaluate the effect of the drug on exercise tolerance. Improved effort tolerance is an important clinical benefit that patients can expect from an inotropic agent.

Where possible, establishment and anecdotal evidence for a change in the quality of life and the demonstration of a change in New York Heart Association class is useful for the inference of efficacy. Perhaps one of the most important contributions of this kind of trial is the acquisition of data on the incidence of adverse effects. Finally, it may be possible, using an emergency protocol, to define patients who are sufficiently improved on therapy to participate in placebo controlled studies. If "compassionate" protocols are designed to varify failure on approved alternative therapy, they may be useful in establishing efficacy of a particular agent in refractory cardiac failure.

The design of controlled studies is less complex. As in the case of the emergency or compassionate studies, a period for baseline measurements is essential. This

is usually followed by a dose ranging period to define optimum therapy. At this point, there is a diversion between the controlled trial and the uncontrolled trial. Randomization to alternative therapy and placebo in one group and alternative therapy and the drug in the other is essential to the format of the controlled trial. There are four possible kinds of controlled trials. The design that is most appropriate depends on the particular agent and the types of patients to be studied. There is little doubt that the administration of drug to one group and placebo to another in a parallel design is an acceptable study format. It might be that the use of a control group and a drug group with crossover is appropriate in certain settings and might even be desirable. On the other hand, when dealing with groups of patients in whom the prolonged use of placebo raises ethical questions, the use of randomized drug withdrawal or the introduction of placebo pulses of varying durations is an alternative approach. This is especially true in situations where the drug is generally considered to be effective and its continued administration believed essential to patient welfare. This would make recruitment to classical controlled trials difficult.

In this situation, randomized withdrawal or the introduction of placebo pulses can be a justifiable means of demonstrating the continued efficacy of the drug in individual patients. At the same time the use of the placebo "pulse" or the use of the randomized withdrawal can be important in establishing efficacy if patients uniformly deteriorate when the drug is withdrawn.

A number of technical problems need to be considered when organizing a controlled trial.

First, it is important to define the population. New York Heart Association classification is one way of defining the population. There are problems with this classification in that ordinary activity must be carefully defined. What is ordinary activity for one person might constitute an unusual effort for another. One also should define symptomatology. It is mild shortness of breath or dyspnea resulting in a inability to function.

Secondly, hemodynamic parameters can be employed in defining the population under study. Minima and maxima

for cardiac output or index might be established. Definition of acceptable pulmonary capillary wedge pressures, ejection fractions or various non-invasive parameters can limit either the severity of illness or the trivial nature of symptoms and so result in relatively homogeneous patient population.
Exercise testing can also be utilized in defining the population. The use of exercise testing involves the establishment of minimum or maximum performance standards on a particular exercise protocol. Which type of protocol to use in assessing response to therapy of patients with congestive heart failure is a question in itself. The standard "Bruce protocol" which is widely accepted for the diagnosis of ischemic heart disease may not always be an optimum protocol for establishing drug effect. It is a relatively severe protocol with rapid changes in the grade, and speed of a treadmill. This may constitute an excessive burden for a patient with significant heart failure. Various modifications of the Bruce protocol may permit more precise definition of patient populations and demonstration of even subtle long term drug effects.

"Alternative" therapy for the control group needs to be

defined. Control therapy may be placebo. It can be salt restriction alone. It can be salt restriction plus digitalis, or salt restriction plus digitalis plus a diuretic, with or without approved vasodilators. Whatever the control therapy, one would be best advised to have the same control therapy for all patients. The type of control regimen is usually defined by the questions being asked in a particular trial. If one is trying to compare a particular drug to digitalis, obviously digitalis would need to be employed in the control group, but not in the treatment group. If the goal is to establish that an experimental drug has a beneficial effect in patients already on digitalis and salt restriction, obviously digitalis need not be excluded from either group.

A number of the parameters can be employed in the demonstration of efficacy in heart failure. It is reasonable to try to obtain the most reliable and reproducible data. Clearly, the data obtained from invasive studies such cardiac index or output, pulmonary capillary wedge pressure, and changes in cardiac rate are most important especially for demonstrating short term efficacy. The measurement of

exercise tolerance is extremely important especially in establishing effectiveness in the long term. A change in New York Heart Association class, when employed in a placebo controlled double blind study is another useful parameter. However, this type of organized anecdotal data lacks sensitivity. Some of the other less sensitive parameters are phonocardiographic systolic time interval changes, echocardiographic measurements or changes in radionuclide ejection fractions.

Finally, there are a number of safety studies that should be addressed when dealing with cardioactive drugs in the heart failure population. These safety studies include ambulatory electro-cardiography. This is helpful in determining whether a particular agent results in an augmentation of ventricular or atrial ectopic activity, alters atrioventricular conduction or results in pauses, severe bradycardia, heart block, etc. Similarly, electrophysiologic studies are important to predict the effects of a particular drug or combinations of drugs on atrioventricular or intra-ventricular conduction.

Standard laboratory determinations are important to

demonstrate the effects of drugs and hematologic and biochemical parameterss, especially liver, and renal function.

Finally in trying to predict what approach regulatory authorities might take at during the approval process, it is reasonable to assume their attention will focus on a demonstration of short term efficacy; on a demonstration of long term efficacy, and upon a demonstration of long term safety. The approval process must assess the risk benefit ratio and the availability of alternative effective therapy.

Dr. Cohn: I have asked Dr. Martin Schlepper from West Germany join the panel. Let me take the chairman's prerogative and make two comments that I think address the importance of control trials as Dr. Levitt has already made clear. I think one has to be aware of two facts: number one, although heart failure is a terrible disease in terms of mortality, the course of left ventricular dysfunction and symptoms is not not necessarily inexorably downhill, so we should not confuse the fact that the mortality rate is very high with the presumption that mortality is preceeded by worsening of left ventricular function in the untreated or traditionally treated patient. Therefore, I think the need for control trials is very obvious. One cannot assume, because the patient gets better on a therapy that it is a drug that has done that, because we are all periodically impressed with patients who seem to go through a period of stable if terrible, cardiac performance and actually improve to the point where they are back functioning again, without necessarily the intervention with a miraculous drug or with the cessation of a drug which appeared to be very effective (the effective drug was stopped and by God the patient seemed to do very well.) I think you must have control trials. Dr. Schlepper did you have a point that you would like to make at the outset.

Dr. Schlepper: I can only add some data to yours, about ARL 115BS when used in human beings. It is quite true that it can't be blocked by beta receptor blockers but it is blocked by verapamil in humans too, and it doesn't show any signs of tachyphylaxis when given chronically to a patient with, for example, cardiomyopathy. We were most impressed by the fact that rise in cardiac oxygen consumption during chronic or acute treatment in patients with coronary artery disease seems to be offset by the decrease in left ventricular end diastolic pressure, so that the subendocardial layers may be subject to a

better circulation than before.

Dr. Cohn: Does the left ventricular size go down with chronic therapy too?

Dr. Schlepper: That is correct. Left ventricular size goes down, and in patients in whom angina pectoris could be reproducibly induced by ventricular pacing that was no longer the case after the administration of 115BS, although oxygen consumption went up.

Dr. Cohn: Do you have any control trials of ARL 115BS in Europe?

Dr. Schlepper: We induced angina pectoris and then looked at regional wall movement and at the region of or myocardial failure. We then tried to induce angina again in the same patient and could not.

Although these new drugs don't seem to have any arrhythmogenic properties, I still wonder whether we are putting an undue burden on the already hypertrophied myocardial cells or whether we really improve their performance by administering the drugs, although we get better pump functioning.

Dr. Cohn: That is the big question and will only be resolved when we have an effective drug that we put into a large scale study I guess.

Dr. Henis: A few years ago much was made of the belief that vasodilator treatment of heart failure was more beneficial than inotropic treatment, in that it did not increase myocardial oxygen consumption, important because at least in this country, many if not most patients have their failure on the basis of coronary artery disease. I didn't hear much about that today. I didn't even hear it mentioned as perhaps a desirable characteristic of an agent for treatment of failure. I ask the panel to comment on this. Do you still view this supposed benefit as real? An aspect of this question directed towards Dr. Sonnenblick is: for any degree of effect on determinants of myocardial oxygen consumption, (that is, a heart rate, contractility, etc,) is there anything to indicate that drugs like amrinone have some kind of special oxygen sparing effect? That is, perhaps are more efficient in

utilizing oxygen in the myocardium?

Dr. Sonnenblick: Let me first make a point about the physiology. There is a certain profound misunderstanding in the literature of the work that I did. Looking at the determinants of oxygen consumption, the most important one is the tension in the wall - profoundly most important, maybe 80% of the problem, and that is due to the size and due to the pressure. Second is the heart rate, the number of times you turn on the process. Lastly is the contractility and it is very, very difficult to demonstrate contractility effects independent of these former two, (maybe at the 5-10% level). On an absolute scale, contractility is a very small determinant, although important. There have been a number of studies on catecholamines like dobutamine or done on digitalis, or done on anamirinone (well cited, and I know of no alternative data) that show that when you give an inotropic agent to a normal heart and the heart rate goes up and the contractility goes up, the oxygen consumption goes up. Uniformly (in every bit of data I know and I know of no alternative data), when you give an inotropic agent to a failing heart, the size of the heart goes down and that completely offsets any wastage of oxygen that might have resulted from the improved contractility, and (in man and animals), the oxygen consumption of the myocardium goes down. This should be stressed, because I think Dr. Henis wonders if there a wasting thing that is causing damage from excess use of oxygen. I know of no literature to support that whatsoever- and the literature is uniform in the opposite point of view. The answer to your question is no.

Dr. Lipicky: Two questions of Dr. Sonnenblick. First, if the hypothesis is true that vasodilators are in fact directing the cardiac output to the wrong vascular bed, how can one account for the observation that one can measure increases in exercise tolerance? Secondly, if one were interested in measuring some index of increase contractility over a long time, what would be an

appropriate measure, if one wanted to do it by other than invasive techniques? Would lactate production or something on that order be an appropriate measure of persistent inotropic activity?

Dr. Sonnenblick: Relative to the improvement in exercise performance, if you consider acute i.e. immediate, improvement in exercise performance, it doesn't occur with vasodilators. Nobody has any data that shows it does. It doesn't with any of the vasodilators, and indeed if the vasodilator doesn't permit a fall in pulmonary wedge pressure so one is less short of breath, for example, hydralazine you don't even get chronic improvement in exercise performance. If you add a factor that allows you to breathe a little better and then you train, you do in time then you see a small improvement in performance with training. Let's take the absolute increases. In the vasodilator literature, the improvement in exercise performance is limited to a minute or two. (I have surveyed all that literature), a modest improvement in exercise performance. It is real, it is significant, it is probably correlated with training, it is very beneficial and we are all in favor of it; however one shouldn't be carried away with how big it is. It is measured in seconds, not minutes, seconds up to 120 seconds, and I think you are familiar with quantitation of that. It requires time and time indicates training, so it is more complex than just improvement of the immediate cardiac performance. The immediate effects are shunting of blood and indeed even dobutamine, which is a very good inotropic agent, shunts blood and you don't improve exercise performance. How do you show a chronic increase in contractility? The difficulty is that all the patients we are talking about have an ejection fraction of 20% to 25%, a large diastolic volume and very small shortening, so if you make a small increase in shortening of the wall, we go along way to improve function. Currently I don't know of an easy way to measure it. I don't know how to measure contractility improvements of modest degree over

a long period of time, and that is where the ejection fraction has kind of let us down on a chronic basis. The noise level is far greater than the sensitivity. I don't know how to do it and I say that with a sense of sadness. I don't know if anybody else has learned better how to do it. Acutely it is easy: you measure dp/dt. Chronically you just cannot prove it, unfortunately. That is why we have fallen back on performance criteria like exercise.

Dr. Altman: A question for Dr. Levitt. You spoke of the ethics. If patients, did poorly, then they could be put on randomized control trials. The question is, when you have a patient on an emergency protocol of I.V. dose- response studies, and the patient improves, what do you suggest for alternative long-term future therapy in these patients? Putting them again in a randomized trial, or what?

Dr. Levitt: First of all, I didn't address myself to the question of randomized trial with intravenous therapy. That is a little bit complicated. If the patient is well enough to go on to oral therapy and if the patient then fails on oral therapy, generally the drug would be withdrawn and there wouldn't be that question. The question arises when one thinks that the patient is doing well, or when one thinks that after a period of doing well the patient stops doing well. Then, in terms of assessing what should be done for that particular patient, one might reasonably place that patient in a program of randomized withdrawal. I am not saying that doing so would provide proof-positive of efficacy, but it would show how that patient does after the drug is withdrawn, certainly constituting some kind of placebo comparison. The argument I was trying to make was that it can be said to be in the patients own interest to have that done. Because, if the patient is doing well, one might be very surprised. Here is where Dr. Temple and Dr. Lipicky and people at the agency have a tremendous advantage over most practicing

physicians. They see what happens when the drugs are withdrawn as part of randomized trials long before it ever gets to the public. What seems to happen is that some patients do very well without the drug, for reasons not at all clear. We can hypothesize what they might be. Certainly, if we accept (and ought to accept) that all drugs are toxins, then what one does with the drug is to basically interfere with some physiological mechanism trying to produce a beneficial effect, but one is also producing toxic effects. A patient is certainly better off without a drug if he can do just as well without it. It is in the patient's interest to define, if he is doing well, whether or not he still needs the drug. On the other hand if he is doing badly, then one really has to do what Ed Sonnenblick did: take the drug away and see if the drug had been doing anything. If the drug was doing nothing for the patient, there is no reason to keep the patient on the drug. On purely clinical grounds, in the patient's interest, one could make a very strong argument for withdrawing drug. If one does it on a randomized basis, then that information starts to be a lot more useful to the people who have to make a decision about whether or not the drug is effective.

Some patients whom one is convinced are doing terrific on the drug can be transferred to a control trial, because one is dealing with a group of responders. Whether one should do control trials just in responders or not, is a question that one can argue about, but certainly patients doing well certainly might be put into a control trial and randomized to treatment or placebo. If they do badly in the placebo group and well in the treatment group, then one has additional evidence for efficacy. It might be considered to be in the patient's interest initially to know whether a particular experimental drug is really doing a job for him or whether he got well or worse by himself.

Dr. Temple: Dr. Sonnenblick, my recollection is that most people who have

studied exercise tolerance with these drugs have not had the wisdom to use an exercise protocol that was less intense and stressful than the Bruce protocol. Thus I wonder if you know from your review of the studies, whether the protocols were comparable with studies of vasodilators, and therefore whether the relatively modest increases in exercise time were comparable to the ones you saw.

Dr. Sonnenblick: They were in the Captopril study, using the Naughton protocol, as we did some of them. I assume that was so in the larger group as it was in the initial 40 patients that I think were the initial model. Whether that applies to all of the vasodilator studies, I am not certain. Certainly, in the hydralazine studies there were a large number done on the Naughton protocol. The Naughton protocol was used fairly early on and is sort of like a poor man's Bruce protocol. It gives you increasing loads which are not entirely related to duration, but it is an increasing load. If a patient is in class 4 heart failure, as Dr. Levitt has often pointed out to me, why not just study him flat and see if you can go on. The patient in class 3 could go on for an awful long time, so for class 2 the Naughton protocol is probably good, and for Class 2, the Bruce protocol would probably be useful. If you don't increase the load in some patients, they will never have a limitation to exercise. As you point out Dr. Temple, I am not certain that the same exercise load is good for all patients. The better vasodilator studies, certainly Dr. Cohn's studies, were all done with the Naughton protocol, which I believe within the past two years it has become fairly standard. This is because with the Bruce protocol, as Dr. Levitt pointed out, you reach a huge load suddenly and you turn everything off, and it is very hard to distinguish anything. To my best knowledge, most are done with the Naughton protocol.

Dr. Temple: You showed a slide showing the effects of withdrawal at a late

stage. Was the measurement made exercise tolerance? Is that what was plotted against time?

Dr. Sonnenblick: Yes, that was exercise tolerance on a Naughton protocol, and all of them responded initially, but as one got on towards a year, they started to show evidence of lessened efficacy, being increasingly tired, and those were the ones chosen to withdraw the drug. That is there are those in which we had a question of persistent efficacy.

Dr. Temple: I see you only picked ones who were doing less well.

Dr. Sonnenblick: Less well, but not necessarily catastrophically poorly. That showed up in their exercise. Most had a deterioration of their exercise capacity maybe to 50% of the maximum that had they had after the initial imposition of the drug.

Dr. Temple: There is another group of people treated for a comparable period of time that didn't show such a decline.

Dr. Sonnenblick: Yes and there are some that tend to do well. This is the thing that Barry and Dr. Schlepper brought out, that it is very hard to tell who will tend to stabilize. It doesn't seem to be predicted by the initial improvement in cardiac performance, which is fairly uniform. Early efficacy is very easy to demonstrate, but it doesn't necessarily tell you what will result in the long run. In other words, it is hard to pick out who will do well and who will not do well. I am sure if Jay were here, he would tell you that he couldn't be sure which 70% were going to die. The stable ones are obviously the 30% who remain alive, but the initial studies don't tend to predict that and one doesn't know why these patients go on. It isn't the initial ejection fraction, which is very bad. How to identify the subgroups, how are they different, we don't know. There are some patients when you take off a drug remain stable for many months, and why that occurs, we don't know.

Dr. Temple: I was getting to a question similar to the one you raised about

cardiac glycosides. That is, while seeming to do something useful, there actually could be something not so good going on. That question seems pertinent because in placebo groups,(not generally followed for a year, I have to say, but followed for somewhat shorter intervals), it is not characteristic for most of them to deteriorate very much in the course of study. Obviously, they deteriorated to certain point and they are going to get worse in the very long run, but over the course of these studies, you don't see such a decline. It makes one wonder whether the drug could have been doing that was something not so good, and the patient getting still worse on withdrawal doesn't answer that question. One could still be worse, inotropically speaking, when the drug is withdrawn, and yet the drug might have been having some overall adverse effect, so it really doesn't answer that question.

Dr. Sonnenblick: The possibility of an adverse effect is always a haunting possibility. On the other hand, I think it is partially a matter of selection. All the patients that we have studied were studied because they were seriously symptomatic at the time they were referred, on digitalis and diuretics at least, and very commonly on vasodilators. In effect they weren't stable or doing well. You rarely study such patients. Certainly, if they are not doing well, their tendency is downhill and to go on and die, so that in effect, there is an emergency situation that enters them. I think we are talking about the patient who is not in quite that phase - let us say, early class 3. There could be a subtle negative effect occurring at the same time that you allow the pump to function better. In the very severe patient, late class 3, or early class 4, I don't think there is stable disease. You are looking at the best that Jay Cohn can do with early class 3 as well as class 4. He has 70% mortality and ours is worse. The Duke group in class 4 has something on the order of 90% mortality in about 6 to 9 months. The mortality in class 4 is

measured in months, not years. Our mortality for the patients who weren't treated for one reason or another is measured in weeks. It is the same group that go on to transplants. They don't remain stable at Stanford, they die. We are talking about somewhat different groups, and if you talk about patients seen early enough, then variability comes in and they wax and wane. Probably in very early disease, one doesn't know whether one makes things better or worse. I would hate to have efficacy for digitalis.

Dr. Levitt: I think that there is another issue, Bob. I think that if we look at the studies that I think you are alluding to, those were 2's and 3's. The question was how one defines a 2 and how one defines a 3. There was only one class 4 patient in the particular studies that I think we have talked about and such patients may not have the same short term 3-month prognosis. I think there is a reason, that it is difficult to mount a controlled study in class 4 patients. I don't think that many institutional review boards would sit still for it. We have discussed this and the reason for introducing the concept of randomized withdrawal and placebo pulses. It may be much more reasonable to say that we should study class 4 patients in order to get cleaner answers faster. It would do a lot more good to a lot more people. I think as the data we have available is not in the same group of patients that Ed Sonnenblick is alluding to, and I think maybe we ought to do something about getting some data in such patients, but my impression is that those are not the patients who do well.

Dr. Temple: Obviously you have to know if you are talking about the same patients, but at least in some of the vasodilator studies, people who were thought to be very sick had prolonged favorable effects, as measured by N.Y. Heart Association status. They at least did not get overtly worse and had modest increases in exercise, but it really is possible they are different enough even within class 4 such that you can be just in it or almost out of

it.

Dr. Sonnenblick: I am impressed with what Jay Cohn said just before he left and what Stu is saying now,that there seem to be subsets we can't identify, that seem to behave differently. The mix in any particular study may lead to trouble with interpretations. This comes back to the reason why one needs to have randomized controled studies as much as possible.

Dr. Sonnenblick: We have purposefully studied the sickest people and I think that our inotropic data is probably based on somewhat sicker people than the vasodilators.

Dr. Reich: I would like to address a question to Dr. Sonnenblick. Concerning your reservations about using the ejection fraction as a parameter, would you say that the disappointing results were generally related to the agent you were studying at the particular time frame, or were you making a broader generalization? For example, would you say there is any role for using non-invasive studies of the ejection fraction in assessing these agents?

Dr. Sonnenblick: It is from experience with a number of different kinds of agents, either the vasodilators or the inotropic agents. When the ejection fraction is very low, in the 20 to 30% range, the changes that one sees are small enough that it is hard to follow them over a period of time and show that they are going in a positive direction. Even if it stays the same, you might have actually been helping the patient because it might have gotten worse if you hadn't had the patient on the drug. In other words, stability may be evidence for efficacy. We continue to do ejection fractions mainly for lack of something else to do as an alternative. The only conclusion I was making was that it is hard to make any sense of positive results from analyzing the data. I don't know whether Dr. Schlepper has seen anything different.

Dr. Schlepper: I have exactly the same experience. We choose patients who

I think I completely agree with Dr. Sonnenblick in saying that if they don't get worse, it might be a sign of efficacy.

Remarks

Arthur Hull Hayes, Jr., M.D.

Commissioner of Food and Drugs

A year ago when I had the pleasure of joining in your discussions of beta-blockers and calcium antagonists, I took the opportunity to share the impressions of a still fairly new Commissioner of Food and Drugs. As I recall, I talked about the subtle but important differences between scientific inquiry in the academic world and in the regulatory environment of an agency like FDA.

I tried to give you my perceptions of the necessary tension that exists between the need for innovation and the need for caution in seeking to exploit new knowledge for the benefit of society. I hardly need say that FDA is often at the very heart of that tension.

I had a few things to say that evening a year ago about how I view the role and responsibilities of the regulator, that that task is to do for the consuming public what it cannot do for itself in terms of assuring the quality, wholesomeness, safety, effectiveness and reliability of products many of which are vital to our welfare.

But at the same time, I suggested that regulation, in the zeal for consumer protection, must not impose arbitrary, outmoded, or unnecessary constraints on the systems that produce consumer goods, systems whose parts range from basic science to manufacturing and advertising. For if regulation overplays its role, everyone loses, the scientific community, the segments of industry that translate knowledge into products, and the public that relies on new goods and services for satisfaction, welfare, and not infrequently, for life itself.

Let me not give the impression that I have come back this evening with nothing more than a rehash of what I talked about a year ago. That is not my intention nor, indeed, would that even be possible. There is a bit of oriental wisdom that says, you can never set foot twice into the same river; it will have changed, and so will you.

And indeed we have seen many changes in the last year, two of which I would like to touch on this evening, changes in the way we intend to pursue the regulation of new drugs and changes in the way people have access to information about the drugs prescribed for them.

Let me turn first to the proposals we have developed to improve drug regulations. Our plan to revise the process by which new drugs are approved for marketing rests on the firm conviction that no drug should be approved by FDA unless and until it has been proven safe and effective by testing against the standards of current science and clinical medicine.

But it is clear to me, as it has been to the many study groups both inside and outside government that have examined the drug approval process, that significant improvements can and must be made to render the process more efficient, less time consuming, less costly to both industry and the taxpayers, and more responsive in bringing safe and effective new drugs to the market as quickly as possible.

The mere fact that the system now in place was devised more than 20 years ago in itself suggests that change may be in order. We have learned a great deal in two decades, and it is time we reaped the harvest of that experience.

For example, new drug applications now average 100,000 pages in length. The majority of that mass of information submitted to FDA by a drug firm in order to obtain marketing approval, is made up of case reports on as many as 3,000 or more individual patients who participated in clinical trials of the drug.

We are proposing that instead of the routine submission of the case reports themselves, sponsors tabulate the data on more concise computer printouts, thereby facilitating review. Case reports will still be required for those patients who die or who drop out of clinical trials due to adverse drug reactions, because those case reports are most likely to reveal significant safety problems. And of course, the remaining case reports will still be available, if needed. This one change would provide the data in a more usable form and would decrease the bulk of a new drug application, an NDA, by as much as 70 percent. Obviously, it would expedite the work of FDA's reviewers, considerably.

We are also proposing to revise the NDA format to include a summary. A comprehensive review of the state of knowledge about the drug, and separate technical sections for the reviewing disciplines within FDA that have to scrutinize the mass of data developed in the course of investigations with the drug. By separating out the clinical, pharmacological, chemical, statistical, biopharmaceutical and microbiological data in a drug application, the sponsor will make it possible for FDA reviewers in

these fields to work on an application concurrently, a considerably more efficient approach than the present one which requires some reviewing disciplines to wait for others to finish.

We have suggested a new appeals process that will allow resolution of scientific differences between reviewers and drug sponsors within 60 days, instead of the indefinite period that such resolutions can consume under the existing system. The new approach would amount to a pledge on FDA's part to reach a resolution through successive appeals by a certain date, and review by higher FDA levels would be automatic for unresolved issues. We believe this proposed change would eliminate the nagging sense that if drug sponsors do not accede to a reviewer's judgment or demands for additional information, an application for approval may literally languish indefinitely in a kind of regulatory limbo.

Another important change concerns the use of foreign data. Although fully half of the NDAs submitted to FDA contain data on experimental studies conducted abroad, our policy at present is that, with rare exceptions, an NDA ordinarily cannot be approved solely on the basis of foreign data. Under the new proposal, we would allow approval of an NDA based entirely on foreign data if the work reported was scientifically valid, had been well conducted by recognized investigators and if the studies and findings were applicable to the U.S. population. While insistence on domestic studies might have had some legitimacy 20 or even 10 years ago, I think we all agree that investigators abroad are fully able today to carry out research that meets our own standards and that can provide valid scientific information on which judgments about a drug's potential use in this country can be based.

We have also proposed tightening the time clock for reviewing NDAs. Although the law specifies that FDA has no more than 180 days to rule on an NDA after it is filed, it has become customary to restart the 180-day clock from the beginning after each amendment of re-submission. Under our proposal, once the 180-day clock starts running, it would be stopped only for the time necessary for the applicant to resolve deficiencies. Unless both FDA and the sponsor agree to an extension, FDA would issue within 180 days a letter either stating that the application is approved or indicating what needs to be done to make it approvable.

Our plans for strengthening the NDA process also include other provisions. For example, a proposal to reduce the requirements for FDA

approval when a drug sponsor intends to make a minor change, such as changing the size of a container, and a proposal to permit individuals to bring limited qualities of unapproved drugs into this country for their personal, non-commercial use.

Finally, we are proposing two important changes designed to increase patient safety. The first is a new procedure for updating an NDA with new safety information while the application is still being reviewed by the agency. This change will ensure that approval decisions, as well as the physician's labeling, are based on the most up-to-date safety information possible.

The second safety-related change involves strengthening the post-marketing surveillance of approved drugs. We will continue to require prompt reporting of serious adverse experiences within 15 days. But we propose to tighten up on the reporting of the remaining drug experiences to 30 days rather than in annual reports. However, we are expanding the universe of reportable events to include any failures of pharmacological action and all suspected drug reactions, including those associated with withdrawal or overdose. In this way, FDA's data base will be kept up-to-date and, if problems emerge, FDA will be able to act promptly and on the basis of more complete information.

Let me diverge here for a moment to offer a special plea to my fellow practicing physicians. Recent events this past summer have reminded us that certain rare adverse reactions can never be detected through clinical trials involving a few thousand patients, but must instead await discovery during the period of mass marketing and use.

FDA/s post-marketing surveillance is largely dependent on the voluntary reporting of drug experiences by physicians like yourselves. Unfortunately, it is well known that such adverse drug experiences are most under-reported. This must change.

If FDA is to provide the public with adequate protection during the post-marketing period, your help is needed. As I will explain further in a moment, voluntary cooperation by the medical community plays an essential part of public health protection.

In summary, I think we have devised a practical, workable approach to streamlining the NDA system and doing so without compromising in any way whatever the basic requirement that approved drugs must be safe and effective. This, the first sweeping proposed revision of the new drug

approval process since 1962, was signed by Secretary Schweiker in June. It has now been reviewed by the Office of Management and Budget and was published for comment in the FEDERAL REGISTER one week ago.

But I hope that you and your colleagues thought the country will give these proposals the closest possible examination and that you will give us the benefit of your criticisms and your suggestions.

It should be obvious that the medical profession and the people whom medicine serves have a major stake in efforts to make the review and approval of drugs as efficient and effective as it can possibly be. As these symposia attest, great, even miraculous strides are being made in the science of pharmacology. We are, quite literally, living and working in the second therapeutic revolution, and I am determined that the drug regulatory system carried out by FDA contribute as fully as possible to the process of bringing new knowledge to the benefit of mankind.

Just as we recognize the importance and necessity of the major drug regulatory reforms that were introduced 20 years ago following the Thalidomide tragedy, so 20 years from now, we and our successors will appreciate that the regulatory reforms adopted in 1982 were equally important and equally necessary. In fact, they will be seen, I believe, as helping to secure the gains that the second therapeutic revolution so clearly offers for medicine and for mankind.

It is a truism, I suppose, that the practice of medicine becomes progressively more complex. Sophisticated technologies, new classes of drugs developed in the aftermath of new discoveries in molecular biology, new and highly refined systems for delivering therapeutic agents precisely to the point at which their action will be effective, these kinds of advances can have the tendency to widen the gap in understanding between practitioner and patient, between the personal experience of disease and the oftentimes all too impersonal efforts to diagnose and treat it.

Yet, we are living and working in an age when people want to have a substantial role in efforts to maintain their own health and to participate in decisions about the health care they receive, a development that makes for better and more effective medicine.

Regrettably, the training that most health profesisonals received as recently as a decade ago, and that many are receiving today, gave scant attention to the role of the patient in his or her own care. Most medical education today provides little, if any, preparation of physicians for a

role in counseling patients about therapy or about making use of the increasingly available sources of drug and other information designed for patients. in point of fact, it was largely because of the increased interest and activity in the broad field of patient drug education that secretary Schweiker and I decided erlier this year to rescind the mandatory patient package insert program that was just then getting under way.

After carefully examining that program and the comments we received in response to our proposal to end it, I concluded that much more could be accomplished through voluntary collaborative efforts by all those groups and organizations that had an interest in, and a commitment to, better patient drug information, the professions, consumers, industry and of course government.

The mandatory pilot program would not have demonstrated the value of patient package inserts and would have deterred the development of equally or more effective means of disseminating patient drug information. FDA's current efforts in patient education are, in fact, directed primarily at stimulating and facilitating professional and private initiatives. I would like to take a few minutes to tell you what we at FDA are doing in this important area.

Last December, when we announced that FDA would propose to rescind the mandatory PPI regulation, I formed within FDA a Committee on Patient Education, known for short as COPE, to coordinate and spearhead government efforts to encourage and assist private and professional patient drug education initiatives.

The Committee is carrying out these main functions:

- identifying new ways to bring information about prescription drugs to consumers;
- encouraging additional private sector initiatives;
- working with health professionals on systems that will facilitate providing more information to patients,
- encouraging the formation of, and serving as a link to, outside organizations that are or intend to become active in patient information systems;
- providing guidelines to, and functioning as a clearinghouse for, firms and organizations that are producing patient information materials or are planning to do so; and,
- alerting consumers and health professionals to the usefulness and

availability of prescription drug information.

We have set about to assemble information on what is happening and being planned in the private sector with respect to patient education. To accomplish that, we have met with many professional, trade, consumer, and industry organizations and firms, including the American Medical Association, The American Academy of Family Physicians, the Society of Hospital Pharmacists, the National Association of Retired Persons, Ciba-Geigy, Hoffman-LaRoche, Biomedical Information Incorporated, the Pharmaceutical Advertising Council, and many specialty societies and consumer groups.

In addition, I have written to literally hundreds of professional, voluntary and private organizations inviting them to provide samples of patient education materials to form the nucleus of a Patient Education Resources Center (PERC). The Center is performing the clearinghouse function I mentioned a moment ago by gathering, abstracting, and making available examples of patient information materials so that organizations interested in becoming active in this field can have the benefit of knowing what their colleagues are doing.

It seems clear that every segment of society that has an interest in, or can contribute to, patient education is getting involved in this activity, some very creatively, others more in the vein of becoming informed.

Among the other initiatives that COPE has under way are:

-A public service advertising campaign to make patients more aware of the need for drug information and of the importance of bringing their drug-related questions to the attention of doctors, pharmacists and other health professions;

-A telephone survey of consumers, pharmacists, and doctors to provide baseline information on levels of patient drug information against which to assess the impact of new and emerging patient education efforts; and,

-close liaison with other federal health programs that can serve both as sources of patient education and as conduits for patient information.

To some extent, of course, our next steps will depend on events and initiatives in the private sector and among the professions. Let me just mention some of them:

The American Medical Association has launched its campaign to have physicians distribute patient medication instructions at the time prescriptions are written. It is based upon a premise, that I believe is accurate, that physicians must persuade those in their profession to become more involved in the education of their patients. The PMIs represent a major program aimed at providing drug information that physicians can pass directly along to patients. PMI's can be tailored to the individual patient's needs and can reinforce the physican/patient dialogue. For all these reasons, I have heartily endorsed that program.

The American Association of Retired Persons is now including patient information leaflets with prescriptions filled through its mail order pharmacy service. This program recognizes the fact that certain groups, such as the elderly who may be receiving maintenance drug therapy, have special informational needs. I'm happy to say that FDA was able to provide assistance to the AARP in drafting those leaflets.

The American Academy of Family Physicians and the United States Pharmacopeia have joined forces to distribute USP information on drugs to patients through family practitioners. I applaud such cooperation between those having responsibility for patients and those with information expertise as the kind of joint effort that will make maximum use of the resources available.

USP is also offering several publications directly to consumers, translating patient information into Spanish, and even exploring material for electronic distribution to home computers and cable television networks.

There are now over 20 consumer-oriented drug information books generally available through book stores and clubs, pharmacies, and other retail establishments. The mere existence of so many such books, and profitable ones I might add, points out the increasingly apparent demand from consumers for information about their medications.

Pharmaceutical manufacturers have produced hundreds of different patient education materials, ranging from simple brochures to elaborate slide presentations and films.

Some have criticized the Federal Government for rejecting a mandatory patient information system in favor of private initiatives. But just look at what is already being accomplished by the private sector, major programs are being implemented by diverse organizations with the finanacial

and logistical resources to carry them out. These developments have encouraged me enormously, and convinced me that voluntarism can work, and that a cooperative effort between government and the private sector will produce more and better information than a single, limited, government-run mandatory program ever could.

It is particularly encouraging to note that many of the organizations that are most active and most interested in patient drug education have joined in the creation of a National Council on Patient Information and Education. The Council, whose chairman is Mr. Paul Rogers, whom many of you remember as the distinguished Chairman of the Health Subcommittee in the U.S. House of Representatives, will, I am sure, be a leading force in stimulating efforts to improve both the sources and the availability of patient drug information.

At its founding conference in Washington just two weeks ago, the Council committed itself to efforts not only to help in the development of patient drug information, but also to make the public more aware of the value of learning about the drug's doctors prescribe for them and of the importance of asking questions. The council also intends to encourage evaluations of the effectiveness of patient drug education programs, a vital undertaking if we are to know ultimately whether or not this initiative can deliver on the great potential it appears to have.

I have taken this opportunity to talk about improving the drug approval process and about working to inform patients about the drugs they take because these two initiatives, albeit from very different points on the horizon, come together in what I see as a common cause. They converge on the objective of enabling medicine, more specifically, the use of drugs, to yield for mankind the great benefit that advancing scientific knowledge has to offer.

To do that requires a regulatory environment that hastens progress without compromising protection. It requires a partnership between patients and health care providers that merits confidence and heightens the prospect for even more effective drug therapy.

I believe we are well along on both paths toward that goal. I can think of no more important ways in which FDA, working with the scientific community, the health professions, industry, and consumers, can fulfill its obligations to all those sectors of society, and to society itself.

The stream of events moves always, and we move with it, changing as circumstances dictate change and opportunity makes change possible.

At the risk of repeating myself, I must say, as I did a year ago, this is an exciting and challenging time to be Commissioner of Food and Drugs, and I am sincerely grateful for the interest and the support of the many friends and colleagues who are here this evening. Thank you.

SYMPOSIUM ON NEW DRUGS AND DEVICES

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