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Fredric Solomon, Delores L. Parron, and P. B. Dews, Editors; Division of Mental Health and Behavioral Medicine; Institute of Medicine

BIOBEHAVIORAL FACTORS IN SUDDEN CARDIAC DEATH

Health and Behavior: A Research Agenda
Interim Report No. 3

Summary of a Conference

Edited by Fredric Solomon, Delores L. Parron
and P.B. Dews

INSTITUTE OF MEDICINE
Division of Mental Health and Behavioral Medicine

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INSTITUTE OF MEDICINE

Advisory Panel for the Symposium on
Biobehavioral Factors in Sudden Cardiac Death

Chair: Peter B. Dews, M.B., Ch.B., Ph.D.
Stanley Cobb Professor of
Psychiatry and Psychobiology
Harvard Medical School

Frances Cohen, Ph.D.
Assistant Professor of Medical Psychology
University of California School of Medicine
San Francisco

Robert Eliot, M.D.
Chairman, Department of Preventive and Stress Medicine and Director, Cardiovascular Center
University of Nebraska Medical Center
Omaha

Regis DeSilva, M.D.
Brigham and Women's Hospital
Harvard Medical School and
Cardiovascular Laboratory,
Harvard School of Public Health

Joel Dimsdale, M.D.
Assistant Professor of Psychiatry
Harvard Medical School
Massachusetts General Hospital

David A. Hamburg, M.D. (ex officio)
President, Institute of Medicine
Chair of Steering Committee for the study, "Health and Behavior: A Research Agenda"

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New England Regional Primate Research Center
Harvard Medical School
Southborough, Massachusetts

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Professor of Medicine
The New York Hospital
Cornell Medical Center

C. David Jenkins, Ph.D.
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Boston University Medical Center

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Alcohol, Drug Abuse, and Mental
Health Administration

Stephen Weiss, Ph.D.
National Heart, Lung, and Blood
Institute
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PREFACE

A Conference on Behavioral Factors in Sudden Cardiac Death was held on August 5, and 6, 1980, at the National Academy of Sciences in Washington, D.C. This symposium was organized by the Institute of Medicine, through its Divison of Mental Health and Behavioral Medicine. Support was provided by the Alcohol, Drug Abuse, and Mental Health Administration and the National Institutes of Health, Department of Health and Human Services. This meeting was the third in a series of six invitational workshops to be conducted over a two-year period, for a study of "Health and Behavior: A Research Agenda." This study is designed to assess the present and potential contribution of the behavioral sciences to our understanding of several serious and widespread public health problems. The goal in this enterprise is to find ways in which both the biomedical and behavioral sciences can be employed to reduce the burden of illness in this country. The conferences will attempt to:

-- direct the behavioral sciences toward a wider range of health problems than the mental health issues with which they have traditionally been concerned;

-- link the biomedical and behavioral sciences with each other;

-- stimulate interdisciplinary clinical research and interdisciplinary basic research.

Under the chairmanship of Peter B. Dews, M.B., Ch.B., Ph.D., Stanley Cobb Professor of Psychiatry and Psychobiology, Harvard University, the Conference on Biobehavioral Factors in Sudden Cardiac Death brought together cardiologists, epidemiologists, and neuro- and behavioral scientists who have worked extensively on biobehavioral aspects of problems related to sudden cardiac death, along with scientists (both biomedical and behavioral) who have not worked directly in this interdisciplinary area of health research. In general, the meeting was an opportunity collaboratively to explore (1) overlapping sets of risk factors and symptom pictures that comprise the sudden cardiac death (SCD) problem; (2) proposed pathophysiologic mechanism for SCD -- both in terms of accrued evidence and promising leads; and (3) observations and research needs in understanding and modifying biobehavioral forces that may contribute to the pathogenesis of SCD. The conference emphasized research approaches that could be undertaken profitably in attempts to integrate relevant biobehavioral research into the health sciences that bear directly on medical care.

Introduction and Overview

P.B. Dews
Conference Chair

Background

"Health and Behavior: a Research Agenda" is the Institute of Medicine project that led to the organization of this conference on the "Biobehavioral Factors in Sudden Cardiac Death." The project arose from a conviction that the behavioral and social sciences are contributing less than they could to improving people's health and well-being. From the earliest days of medicine, physicians have recognized that the behavioral activities and social context of people can profoundly affect their health. The elucidation of the mechanisms of behavioral and social influences on disease have lagged, however, far behind the discoveries about infective, nutritional, degenerative, and even neoplastic mechanisms of disease. Although health professionals have frequently acknowledged the influence of behavioral and social influences on "physical illness," there is a woeful lack of knowledge about the extent of these influences or their mechanisms, even when behavioral factors are believed to be the dominant influences in causing a particular variety of ill-health. Behavioral influences on the pathophysiology of sudden cardiac death (SCD) are not generally regarded as quantitatively major factors, and their contribution will continue to be hard to measure until more is known of mechanisms. SCD is so prevalent, however, that the identification of even relatively minor influences on it, if they can be controlled, would represent a major contribution to health.

Why SCD as a Topic for a Biobehavioral Conference?

In trying to discern avenues of behavioral and social science that may be followed profitably to improve health, a reasonable approach is to select a major health problem that costs millions of man-hours of productive and enjoyable life and to seek behavioral and social contributing factors. In the United States, SCD represents such a major health problem. It was generally agreed at the conference that there are 400,000 SCDs annually in this country; SCDs exceed the deaths from all forms of cancer combined. In addition, SCD occurs at a somewhat younger average age than does cancer, so that its effects on productivity are relatively greater. Few behavioral and social scientists expect rapid, dramatic contributions of their science to medicine in the manner, for example, that the isolation of a succession of infectious agents profoundly influenced late 19th Century medicine. Yet, even a

modest influence on an affliction as prevalent as SCD would represent an aggregate contribution to the human race that may be greater than the abolition of many a rare disease.

The National Heart, Lung, and Blood Institute has had a program of studies on SCD and has conducted conferences on elements of the SCD problem. The present conference is unique in that it is the first to take the biobehavioral factors in SCD as its theme. Biobehavioral factors have been ascribed less importance in SCD than in some "functional" or "psychosomatic" disorders, such as asthma and colitis, because there is concrete pathological evidence of heart disease in most cases of SCD and "functional" contributions often are not obvious. Authorities at the conference agreed that most SCD occurs in individuals with diseased hearts (usually coronary atherosclerosis) readily demonstrable at post-mortem examination, even when the disease had been silent until the terminal episode. With pathologic evidence, it is often argued, one does not need to postulate "functional" contributions.

Yet even the most radical organicist must recognize the contribution of behavioral and social factors to the genesis of the pathology predisposing to SCD. Diet, exercise, and salt, tobacco and alcohol intakes are factors that undoubtedly influence arterial and myocardial pathology--factors primarily behavioral and social in origin. Such determinants are appropriate subjects of attention for the behavioral and social sciences to contribute to the prevention of cardiac disease. We were not primarily concerned, however, with such long-term, predisposing factors in this conference.

The symposium focused mainly on proximate behavioral and social factors in the final episode of SCD; the current and immediately preceding circumstances of SCDs, going back no more than a few days or weeks before the episode. It should be remembered that although the heart is almost invariably diseased in SCD, the type of disease is typically chronic and compatible with many years of active and satisfactory life. Thus, it is entirely possible that for a particular level of pathology, behavioral and social factors may trigger an attack of SCD today, or not for 20 years or more. Thus, we are concerned more with the factors that facilitate the physiological disturbance in a diseased heart, resulting in an arrhythmia incompatible with life, than with the equally legitimate inquiry into the long-term personal and societal factors that had contributed to the development of the anatomically diseased heart.

Biobehavioral Factors

What is being attempted in these brief succeeding comments is to add to the increasing chorus of voices calling for a broadened scope of medicine beyond what it has come to signify to the public, and, as is discussed later, to many within the profession itself. The image of modern medicine is of expensive high-level technology centered around tertiary-level institutions. Medicine in the future must embrace a more comprehensive approach to health, going beyond the mere treatment of disease of infective, neoplastic, and degenerative origin. Of course, public health and preventive medicine have long been concerned with broader aspects of health maintenance and enhancement, but they too have been mainly concerned with physical rather than behavioral and social factors, perhaps largely because the information was lacking on how to intervene effectively in these areas. In recent years, the term "biobehavioral" has become popular to refer to behavioral, and, indirectly, social factors playing a role in the genesis of traditional medical diseases, such as SCD. The term carries with it the implication that the behavioral factors will be studied objectively and quantitatively so that the information collected will be compatible with traditional pathophysiology.

In subject matter, biobehavioral medicine has more in common with the psychosomatic medicine of the 1930s and 40s than it cares to admit. A new term is justified, however, because techniques for analysis of behavioral factors have improved enormously in the last 30 years: the new term emphasizes "behavioral" rather than "psychic" factors. There is no reason why the new endeavors should start with the stigma arising from the relative failure of psychosomatic medicine to fulfill its promise -- a failure, perhaps, largely due to techniques and theories not yet being available for much progress to have been made in solving medical problems. The biobehavioral approach integrates the elements of "traditional" and high technology clinical medicine with the behavioral, social, and psychic elements that heretofore have been relegated either to specialties of their own within medicine (but out of the mainstream) or to other professions traditionally viewed as being "outside" of medicine. Although biobehavioral medicine will not itself become the mainstream of clinical medicine, its findings will be integrated with knowledge of other factors predisposing to, or precipitating, pathology that does constitute the mainstream of medical progress.

An additional contribution to clinical medicine that behavioral science might make is the identification of behavioral patterns and social contexts that determine the level of patient compliance with both programs of prevention of disease and therapeutic regimens; and then to improving compliance.

What is being discussed is one aspect of the essence of preventive care: identification of patterns of behavior which may contribute to the development of pathological physiology and anatomy. Specifically in SCD, success could result in a shift in emphasis in medical care from treatment of patients in the tertiary-level cardiac intensive care unit toward reducing the pathology of the disease through change in patterns of behavior and social context, as well as by more conventional public health measures. Such preventive measures depend on discovering what and how personal and societal factors initiate and maintain activities that contribute directly to the genesis of pathology or at least to increase the risk. For example, what environmental factors combined with background experience produce particular patterns of skeletal muscle activity and neural and hormonal discharges that produce or facilitate hypertension? What societal and personal factors favor obesity? It is only from answers to such questions that effective interventions for prevention can be developed.

Definitions

During the conference, it was emphasized that different professional groups concerned with SCD use different definitions of it. Medical examiners may prefer one definition, pathophysiologists another, and epidemiologists yet another. Certainly, it is legitimate for each group to organize its field of information to facilitate its efforts, but at the same time it is essential to the progress of a biobehavioral effort that groups be able to communicate with one another unambiguously. This is particularly of importance when the immediate goals of the groups differ, although of course the overall long-term objective of all the groups is the same: the well-being of the patient or the prevention of the individual from becoming a patient.

A significant portion of the workshop discussions was on the definition of SCD. It was understood that a uniform definition may not be optimal for specialists in any of the specific disciplines, though it must be intelligible and applicable, perhaps with compromise, in each. Although at times inconvenient, use of this single definition is necessary to avoid misunderstandings in the development of interdisciplinary collaboration.

One definition of SCD is: "death within 24 hours of a 'heart attack' in a previously fully ambulatory person." The element of unexpectedness is implicit in the definition. A person incapacitated by heart disease, and hence not ambulatory, is deemed to be in imminent danger of death. A death under such circumstances, therefore, is not considered <u>sudden</u> cardiac death. Whether or not the individual was previously aware of cardiac

pathology is not relevant to the definition, provided that a more or less normal life was being lived. Use of the vague term "heart attack" emphasizes the multiplicity of prodromal symptoms reported in cases of SCD, often in no way typical of the occurrence of an acute myocardial infarction (AMI). Frequently, no elevation in the ST segment is seen in the electrocardiogram in SCD, while this change is almost always present after an AMI.

An additional distinction was made between instantaneous death, occurring within minutes, and other forms of SCD. Such fine classifications undoubtedly will become more important as both risk factors and pathophysiological mechanisms achieve more precise definition. In the majority of SCDs, death occurs well within the 24-hour limit, indeed, within the first minutes or hours, and the definition was extended to cover death up to 24 hours to permit cases of persons who had not been seen for some hours, for example, overnight, before being found dead to be classed as SCD. While the 24-hour definition may be convenient for medical examiners, some very serious doubts were raised as to whether this definition was optimal for maximizing the homogeneity of diagnostic categories desirable for investigations of mechanism and for epidemiology. Although the conference did not consider itself the appropriate promulgator of a new definition, we urge that some other more durable qualified body address the problem. (See Hinkle, in press.)

Problems for Biobehavioral Approach

Specialists in many disciplines now regard biobehavioral studies with a great deal of caution, if not actual hostility and defense of territory. For example, specialists in fields such as cardiology who rely heavily on objective measurement of unambiguous variables frequently view biobehavioral aspects of disease as being less than credible, because historically the behavioral sciences have used multiple, vaguely defined variables and concepts; clear cause and effect relationships have rarely been demonstrated. Although the question of credibility may, at times, be directed appropriately toward a particular researcher or research effort in cardiology or elsewhere, the lack of credibility discussed here is the blanket dismissal of the subject matter of one discipline by another discipline. Again epidemiology has only occasionally assessed the contribution of behavioral factors to the development of diseases. Some medical disciplines such as dermatology or psychiatry have shown a greater willingness to deal with multiple causative factors and non-physical etiologies. With regard to the "harder" disciplines, however, progress toward acceptance of biobehavioral factors will come only from studies that provide inescapable evidence of the importance of biobehavioral factors. Plausibility, persuasiveness, and stridency will not suffice. It behooves

behavioral sciences in relation to medicine to develop objective, unambiguous definitions and measurements and to draw conservative conclusions that can be defended in the face of skepticism.

Much discussion at the conference centered on this need for a new, interdisciplinary perspective and coordination of efforts in SCD research. The conference itself was judged by the planning committee to have provided an important step in establishing a biobehavioral contribution on the SCD topic. Increasing fragmentation has been the characteristic of research efforts in cardiovascular, neuro- and behavioral biology for the past two or three decades. While this subdivision of specialties is to some extent necessary as the complexity of this area of SCD research increases, the efforts of these subdisciplines on specific problems provides only partial answers to the problems. As the various research subdisciplines have grown smaller, they have also grown apart. Thus, the need for integration of these efforts, as well as a system for their continuing assessment, becomes more essential.

Consensus emerged, however, that although some of the etiologic factors of a given disease may be thought to be behavioral, interdisciplinary discussion may have to be focused initially on known medical features, in order to sufficiently delineate how behavioral factors might operate. When a condition has been accurately defined in traditional medical terms, interdisciplinary studies can inquire more profitably into the social and behavioral factors contributing to the pathology. Such an approach may be especially necessary if biobehavioral investigations are going to share the funding resources available for study of a particular pathology where the justification of behavioral investigation must be made in conventional medical terms.

Mechanisms

There was very good agreement among participants on many basic medical facts about SCD. As mentioned before, it occurs overwhelmingly in people with diseased hearts. It occurs primarily in people of mature years, being rare below the age of 40 and not common below 50. Young athletes do occasionally die of SCD, and such instances receive disproportionate publicity leading to a popular impression they are a common form of SCD. They are not. To the extent that SCD occurs in older, diseased hearts, it is not a mysterious disease.

By far the most common final occurence in SCD is ventricular fibrillation, which is incompatible with a life-sustaining cardiac output. This arrhythmia, however, may be reversible with electrical defibrillation. Certain rhythm disturbances, such as complex

premature beats, may presage ventricular fibrillation. Three types of factors may precipitate the potentially fatal arrhythmia:

1. factors related to the load on the myocardium, including volume as well as pressure demands

2. direct nervous influences on the heart through the autonomic nervous system

3. blood-borne chemical influences which are legion and include: oxygen and carbon dioxide pressures; potassium and calcium; dextrose or lack thereof; hormones such as catecholamines, angiotensin, and thyroid, sex and pituitary hormones; dietary intakes of alcohol and other substances; as well as nicotine and carbon monoxide from tobacco smoke.

We may regard these mechanisms as final common paths whereby behavioral and social factors can influence the heart. It becomes necessary, therefore, to describe the behavioral and social factors that may invoke these common paths:

1. the behavioral activities themselves can be factors. For example, exercise influences the load on the myocardium; contributions of static and dynamic activities of skeletal muscles determine the relative volume and pressure demands on the myocardium. Besides the direct hemodynamic effects of skeletal muscle activity there are complex reflex effects. It is possible that as the full physiological impact of skeletal muscle activities is elucidated, it will be found that the great preponderance of endocrinological influences, including catecholamine levels consequent upon behavioral and social factors, will be mediated through skeletal muscle involvement.

2. behavioral activities involving ingestion of food, drink, smoke and the like.

3. other factors.

Risk Factors and Pathogenesis

While it is clear that coronary heart disease is the usual underlying pathological condition for SCD, it is unclear why certain diseased hearts are incited to rhythms incompatible with life. The identification of precise psychosocial and behavioral risk factors for the development of SCD is lacking at the present time. Epidemiological studies, however, may point to important associations between such risk factors and the development of SCD.

Predictors as such, of course, give stochastic rather than mechanistic information about a phenomenon such as SCD. While epidemiology eventually may provide circumstantial evidence establishing a causal relationship, simple identification of a predictor does not establish it as a cause. Obviously, if the predictor is not causally related to the disease, changing the risk factor may have no effect on the progression of a syndrome such as SCD. For example, limb skin with ingrained coal particles may be a good predictor of risk of "black lung" disease, but removing all the coal from the skin will have no influence on the progress of the lung disease. Predictors of "high risk" may still be useful, however, even if they have no direct causal significance. With respect to SCD, they may help tell us who should not be airplane pilots and who should arrange to have cardiopulmonary resuscitation available.

Increased risk of SCD has been found with present and past heavy consumption of alcohol, with self-reported depression and anxiety, and with positive responses to questionnaire items such as, "I work under a great deal of tension." It is important to note that the last named predictor is a positive response to the question, not an independent assessment of whether the individual has a lot of pressure on the job. The latter has not been shown to be a predictor, far less to be a causative factor. A demanding job and physical labor may actually be helpful rather than harmful. Inevitably, our conference discussed the role of stress. Stress is a term that covers a wide variety of undoubtedly real phenomena, but it is a term which is in far greater need of clarification of definition than is SCD. It is often not clear whether the term refers to situation or to response. Surely, effects which some people would attribute to stress do contribute to SCD, but whether there is any unitary component to the various phenomena various people call stress has not been demonstrated and is, indeed, highly unlikely.

A negative correlation of SCD with increasingly high socioeconomic class and level of education has been demonstrated in this country and industrialized Europe. The reverse is true in certain developing countries for mortality rates from heart disease. (Similarly, opposite relationships have been reported for obesity and social class in industrialized vs. developing countries.) Obviously, there is no single consequence of relative affluence that is a predictor of SCD.

In predicting imminent SCD, we are currently tantalized by having tentatively identified a number of premonitory symptoms, but the symptoms are common and non-specific and we have no clue as to when they are clinically predictive. Retrospectively, people describe being more fatigued or sleepy in the days and weeks before

their attack. A disproportionate number have actually consulted their physicians within a few weeks of SCD but for a variety of concerns, from which no useful predictor has thus far emerged. In these cases, the active involvement of primary care physicians in looking for predictors is urgently needed. Far too many victims of SCD have been buffeted by a series of extremely rare, perhaps once-in-a-lifetime, calamitous events in the days before their attack for the coincidence to be a matter of chance; but, again, calamitous events are far too common for every potential victim to be placed under continuous surveillance to abort a possible SCD.

Opportunities for Research

It is no surprise that the conferees were able to identify lines of research that could be developed in every discipline represented at the conference. What surprised many, however, was that a great deal of highly relevant research could be performed with presently available techniques--that is, work that does not have to wait for new technical developments. In view of the great magnitude of the problem of SCD and the high likelihood that research will lead to means of substantially attenuating the problem, it is unclear why there is not a greater national sense of urgency to conduct research on the subject. The lack of concern about the problem of SCD is particularly perplexing when compared to anguished concern over some vanishingly small risks of cancer from many environmental hazards. Compare, for example, the public concern over effects of environmental microwave radiation, which has not been shown to have seriously damaged a single individual, with the concern for the causes of a condition that kills several hundred thousand Americans each year.

Cardiovascular neurobiology

Study of the effects of the vagi and cardiac sympathetic nerves on the heart dates from the earliest days of experimental physiology and pharmacology. Research in these disciplines has been thorough and extensive, but study of how the various imputs are integrated in the central nervous system to determine outflow down the final common paths has lagged far behind. One reason for the delay is that neurophysiological techniques competent to address these particular problems have been a relatively late development. Such studies are now possible, however, and a major effort in cardiovascular neurobiology would seem to be an enterprise of great importance. While work is ongoing at present, it is not commanding support in proportion to its potential contributions.

Within the heart itself, there are many crucial, unanswered questions. Among them, for example, is the genesis of coronary

spasm, which may, in itself, constitute a precipitating factor in SCD.

Cardiovascular psychobiology

Much of our current knowledge about cardiovascular reflexes and integration has come from studies on anesthetized dogs and cats. Such studies have provided an essential background, but must now be extended to awake, behaving animals. Of the many unanswered questions the most obvious are: How do behavioral activities modulate cardiovascular function? What are the mechanisms? Techniques are available today that could be applied in a large scale national effort in this area, rather than only in the scattered, though dedicated, efforts of a few laboratories. The foresight of the National Heart Lung and Blood Institute in establishing a system of Regional Primate Research Centers has provided an admirable basis for the logistic support of such a major effort.

We also must ask how patterns of cardiovascular reponse to behavioral and social situation differ between human beings. How are the different patterns related to cardiovascular disease in general, and to SCD in particular? How do different patterns of behavior produce different cardiovascular effects and how are the different patterns of behavior occasioned? What are the physiological mechanisms?

The term "intense experience" was used at the conference and is to be preferred to the traditional term "emotion." No one is likely to overlook the necessity of specifying the nature of the experience when one talks about an "intense experience," while "emotion" may slip by unelaborated and is then quite uninformative. What provokes "intense experiences" in individuals? What varieties of this factor are there, and what are their cardiovascular consequences?

Again, there is interest and work being performed in the field at the present time, but much less than would seem appropriate for the magnitude of the problems.

Cardiovascular sociobiology

Most of our information on social factors in SCD comes incidentally from epidemiological studies or from clinical observations. The indications are that social factors may be enormously important. The few studies in experimental animals support the indications from humans. The rudimentary state of the field is reflected by the limited attention it received at the

conference. A specially designated program of funding is probably necessary. New departures are needed in the form of studies designed specifically to address biobehavioral questions.

Epidemiology

The thrust here appears to be for wider application of existing approaches rather than for the necessity of radically different ones. Cardiovascular disease seems to receive proportionally less epidemiological attention than many less devastating or prevalent diseases. The recent controversy over the correlation between cholesterol intake and coronary heart disease vividly illustrated how little we really know about even such comparatively easily assessable features as diet and cardiovascular disease. What seems to be needed, rather than radical new approaches, is more studies -- especially studies in which biobehavioral questions dictate the design.

Conclusions

Perhaps the most succinct summary of the entire conference as well as of the establishment of a biobehavioral component in SCD research that it represented was submitted afterwards by Louis Cohen, professor of medicine at the University of Chicago. He wrote to assert four conclusions from the conference and to make a proposal for a mechanism by which the biobehavioral sciences could make a much needed contribution to solution of the SCD problem:

1. Sudden cardiac death is a major health problem.

2. The nervous system control of cardiac function is an important participant in SCD. The evidence is not small that the central and peripheral nervous systems affect cardiovascular function, and thereby produce arrhythmias, conduction disturbances, and hemodynamic impairments that lead to sudden death.

3. The data base concerning this neural-cardiac relationship is multidisciplinary and fragmented. It is distributed among many disciplines: cardiology; pathology; neurology; the biobehavioral sciences; psychiatry; and epidemiology, to list some. Some of these disparate efforts have gone as far as each can go, alone.

4. Biobehavioral scientists must work in collaboration with cardiologists and neurologists if the biobehavioral sciences are to contribute to the solution of the problem

> of SCD. The biobehavioral sciences have not generally attained a legitimacy equivalent to that of the other disciplines. Part of this may be inherent in the methodology, but part is inherent in their relative isolation from the other disciplines. Nevertheless, the evidence is substantial that the reaction of the human to his environment (external and internal) has impact on the heart through neural and humoral mechanisms, which alter an individual's susceptibility to sudden death. The best manner in which the biobehavioral sciences can work to help in a solution to the problem of sudden cardiac death is to work in an interdisciplinary manner with cardiologists and neurologists. This will be the means by which these groups can be mutually educated in the other's skills.

How best to implement these goals and to foster the collaborative research so urgently needed? Conferees reaffirmed the necessity of federal agencies providing appropriate review and adequate funding for investigator-originated research in this interdisciplinary area. An additional approach, favored by Dr. Cohen and others, would call for policy decisions to be made both in funding agencies and in academic circles to bring diverse disciplines together "for this common purpose." Guidelines for the funding of working groups or committees at, perhaps, 10 universities would require interdisciplinary educational, research and clinical efforts to deal with the problem of SCD. The object would be the mutual education and interaction of cardiologists, epidemiologists, neurologists, psychiatrists, basic biomedical scientists, and behavioral and social scientists would mobilize their collective skills.

One can be as sure as one ever can in such matters that the investment in such research efforts would be repaid abundantly by a significant impact on the prevalence of sudden cardiac death.

THE CLINICAL AND PATHOLOGICAL SYNDROMES OF SUDDEN CARDIAC DEATH: AN OVERVIEW

James C. Buell, M.D.
Robert S. Eliot, M.D.

"One moment here, the next she trod,
the viewless mansions of her God ..."
John Henry Newman

Some 700,000 individuals die annually of heart disease and of this group 450,000 experience sudden cardiac death within 24 hours (Cobb et al, 1980a; Lown and Graboys, 1977a). Of all coronary deaths, 65 percent are sudden (Lown and Graboys, 1977a) and in nearly 25 percent of cardiac deaths the presence of clinical heart disease is first indicated by sudden death (Kuller et al, 1966). Sudden death is the prime cause of mortality for individuals aged 20 to 64 years and almost two-thirds of coronary heart disease deaths occur with 24 hours of symptom onset. Sudden death occurs far more frequently in men than in women (Kuller et al, 1966; Wikland, 1968). Although the total number of cases increases with age, the fraction of all coronary deaths that are sudden and unanticipated is higher in the young adult male than in the older male (Croce et al, 1960). Between the ages of 50 and 60 years, the incidence of sudden death from coronary heart disease per 1,000 subject is approximately 2.0 for white males, 1.3 for black males, 1.1 for black females, and 0.5 for white females (Kannel et al, 1966; Weinblatt et al, 1968; Kuller et al, 1967).

Nearly 75 percent of all sudden deaths occur at home, eight to 12 percent occur at work (Kuller et al, 1966, 1967; Wikland, 1968), and only two to five percent have been preceded by vigorous physical effort (Spain, 1964). Death is usually attended by ventricular fibrillation and/or tachycardia in 75-80 percent of cases, with bradyarrhythmia or asystole attending 16-25 percent of cases (Adgey, 1969; Iseri et al, 1978). In instantaneous death, approximately three-fourths of the victims have been found to have advanced coronary heart disease (Spain et al, 1960; Kuller et al, 1966; Reichenbach et al, 1977). However, sudden arrhythmic death may also be seen in Morgagni-Adams-Stokes syndrome, aortic stenosis, floppy mitral valve syndrome, primary myocardial disease, acute

myocarditis, coronary embolism, and inherited susceptibility to sudden death syndrome including prolonged QT interval syndromes (Doyle, 1976a).

A key point to recognize is that time-frames importantly influence what is seen at post mortem examinations (Friedman et al, 1973; Cobb et al, 1980a). The majority of sudden cardiac deaths occur in seconds to minutes. However, if one allows a definition to include up to 24 hours from the onset of symptoms, the representation of acute myocardial infarction and pump failure becomes relatively greater than in instantaneous death. The majority of sudden cardiac death cases will occur in the earlier time frames of seconds to minutes: they are out of hospital; there is little or no warning of impending death, and the mode of exodus is predominantly arrhythmic rather than pump failure (Figure 1). This discussion will focus on the early time frame of seconds to minutes, since it represents the majority of sudden cardiac deaths.

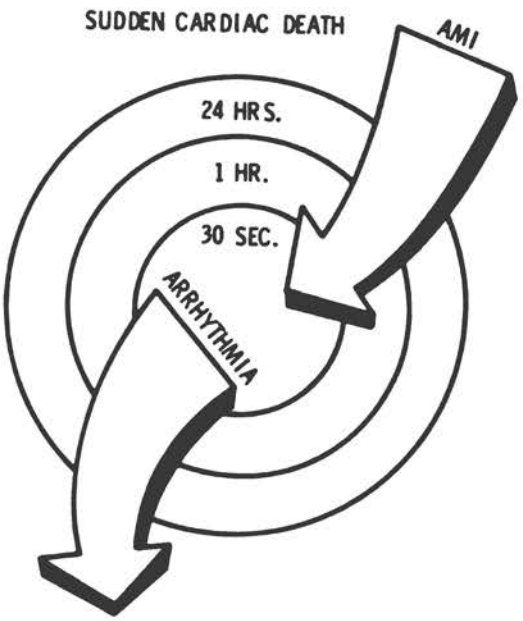


Figure 1

Clinical Experience with Resuscitated Victims

With the advent of effective cardiopulmonary resuscitation and its implementation in the community, investigators have the opportunity to review clinical antecedents and the natural history of events leading to sudden cardiac death. Cobb et al (1975,1978,1980a) have published such studies and they yield some important insights (Figure 2). One can see that of those resuscitated and taken to the hospital, approximately 20 percent will evolve an electrocardiographic acute myocardial infarction (Cobb et al, 1975). Only 35 percent will even show an enzymatic change consistent with myocardial damage (Cobb et al, 1978). In other words, some 80 percent of those experiencing sudden cardiac death have not sustained an acute myocardial infarction. Furthermore, of those who convalesce and are released from the hospital to home, the recurring sudden cardiac death rate is approximately ten-fold greater in those not experiencing an acute myocardial infarction in association with the original episode of sudden cardiac death (Cobb et al, 1978). The point to be made is that sudden cardiac death is not synonymous with acute myocardial infarction. Neither is acute coagulation necrosis the major villain either clinically, pathologically, or prognostically.

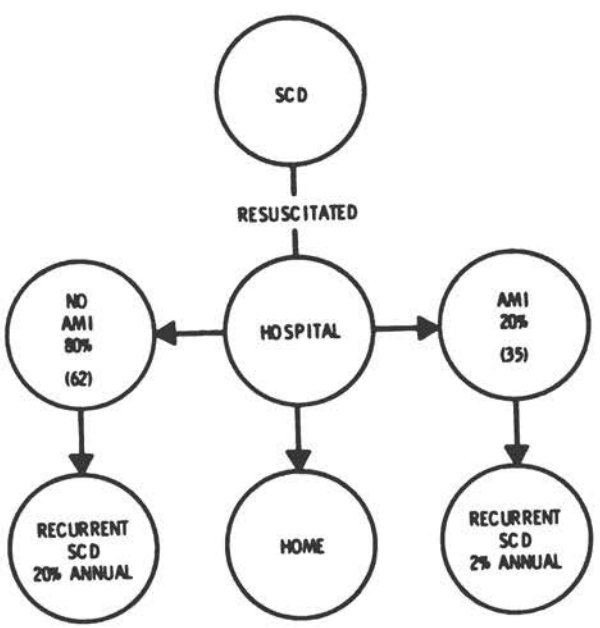


Figure 2

On the other hand, the majority of subjects will be middle-aged men, they will have coronary artery disease at autopsy, and the presence of coronary disease should not be minimized. In the clinical setting, ventricular wall motion abnormalities and discoordinate contraction/relaxation patterns of the ventricle have been found to be associated with a propensity for life- threatening arrhythmias and sudden cardiac death (Dudel and Trautwein, 1954; Kaufman and Theophile, 1967; Weaver et al, 1976; Goldberg, 1977). Of coronary heart disease subjects presenting with sudden death, approximately three-fourths will have had cardiovascular symptoms or signs prior to the episode of out-of-hospital ventricular fibrillation; while in the remaining quarter, cardiac arrest with ventricular fibrillation will be the initial manifestation of coronary heart disease (Cobb et al, 1980a). Recurrent ventricular fibrillation tends to correlate with a history of remote myocardial infarction, prior congestive heart failure, and the finding of complex ventricular arrhythmias on ambulatory ECG monitoring (Cobb et al, 1980b). These all appear to be independent predictors for recurrences of ventricular fibrillation. Univariate predictors of recurrence include male sex, abnormal left ventricular function, and extensive coronary artery narrowing (Weaver et al, 1976; Cobb et al, 1978). Nevertheless, acute myocardial infarction and acute coagulation necrosis do not appear to be predominant contributors to the acute event (Reichenbach and Moss, 1975; Baroldi, 1975).

In looking at histologic findings, Baroldi et al (1978,1979) have studied 208 witnessed cases of people dropping dead and compared them with 97 accidental death cases (Figure 3). As can be seen, survival time in witnessed cases is less than ten minutes in the vast majority of them. If one considers significant vessel obstruction as greater than 70 percent in a coronary artery, the majority of these people do have hemodynamically significant obstructive disease; that is, 70 percent or more. Conversely, 25 percent of the population does not have hemodynamically significant obstructive disease. The histopathology is also interesting in that acute occlusive thrombosis and coagulation necrosis appear in an incidence of 15-17 percent in this series. These findings for acute myocardial infarction are quite similar to Cobb's (1980a, 1980b) experience in a successfully resuscitated population. Baroldi et al (1979) divided their population into expected and unexpected sudden deaths. Expected were those with antecedent history of angina, dyspnea, paresthesia, or vertigo; those with sudden and unexpected death were classified as having no antecedent prodromata as related by careful interviews of witnesses and members of the family according to a specific protocol.

BAROLDI 208 SCD CASES

SURVIVAL TIME	
< 10 MIN.	73%
10-60 MIN.	23%
> 60 MIN.	5%

VESSEL	70% OBSTRUCTED
1 VESSEL	25%
2 VESSEL	29%
≥ 3 VESSEL	21%
	75%

HISTO PATHOLOGY

ACUTE OCCLUSIVE THROMBUS	15%
COAGULATION NECROSIS	17%
HEART WEIGHT ≥ 500 gm.	42%
FIBROSIS	81%
UNIQUE COAGULATIVE MYOCYTOLYSIS	72%
WITH COAGULATIVE NECROSIS	86%

Figure 3

Compared to the 106 sudden unexpected death subjects, examination of 102 sudden expected death subjects showed a significantly higher incidence of myocardial fibrosis, a greater frequency of pathologic heart weight, a higher frequency of maximum degree of stenosis (greater than 90 percent), and triple vessel involvement suggesting a more chronic process. Major histopathologic findings appeared to be cardiomegaly or heart weight of greater than 500 grams. Fibrosis was an overwhelmingly prevalent finding, suggesting that some sort of inflammatory process, at least in the past, had been ongoing. The unique acute lesion was that of coagulative myocytolysis, seen in 72 percent of the cases without acute myocardial infarction and in 86 percent of cases in association with coagulation necrosis. Coagulative myocytolysis is the most prevalent acute lesion seen in sudden cardiac death, and is also seen in those dying of head injuries and pheochromocytomas (Connor, 1968; Baroldi, 1975). It can be experimentally produced in animals by pharmacologic injections of catecholamines. Coagulative myocytolysis appears to represent a hyperfunctional type of necrosis in which clumping of contractile proteins produces contraction bands seen around the intercalated disc. These lesions come on swiftly, in a matter of seconds to minutes, and they go away within 24 hours or so, leaving only a pattern of empty sarcolemmal tubules. This is

subsequently replaced by a patchy myocardial fibrosis and there is no trace of what the initial lesion was at that time. In contradistinction, the hallmark of acute myocardial infarction is coagulation necrosis as a consequence of ischemia. The histologic pattern seen here is a thinning of myofibrils and elongation of nuclei at its earliest stage, representing a hypofunctional state. Coagulative myocytolysis or hyperfunctional necrosis may be seen in mugging victims dying suddenly in the face of trivial trauma, in monitored aircraft test pilots who have lost control of the aircraft and die suddenly before impact, and in victims of pheochromocytoma.

Histopathologically, therefore, there is an overlap of sudden cardiac death syndromes represented by two entities. At one pole is acute myocardial infarction, frequently attended by chest pain and histologically showing elongation and thinning of nuclei and myofibrils. At the other pole is a more frequent presentation of sudden cardiac death with little or no warning attended at autopsy by coagulative myocytolysis and by the presence of anomalous contraction bands.

Clinical Pathological Factors

Thus, an overview of sudden cardiac death appears to involve contributions from several destructive factors. Certainly one of the most prevalent is that of coronary artery disease (Figure 4). In terms of sheer numbers, coronary artery disease is found in the majority of sudden cardiac death victims and its progression and development appears to be fostered by a menu of traditional risk factors (Liberthson et al, 1974; Baum et al, 1974).

The second major factor is obviously that of electrical instability because the mode of exodus in victims of sudden cardiac death is uniformly electrical. Here, risk factors include ectopic activity, various types of rhythm disturbances, conduction defects, family history, and QT prolongation (Figure 5). Although familial sudden death syndrome or QT prolongation is rare, it is important in that it appears to be a Rosetta stone linking central nervous system activity with the production of arrhythmias and sudden death in these individuals.

The third major pathological component is that of myocardial disorders and it appears that it is through this mechanism that coronary artery disease exerts its influence by rendering myocardium vulnerable, jeopardized, or blighted (Figure 6). Among the notable epidemiologic factors here is alcohol abuse as a myocardial toxin. The majority of patients experiencing sudden cardiac death have one

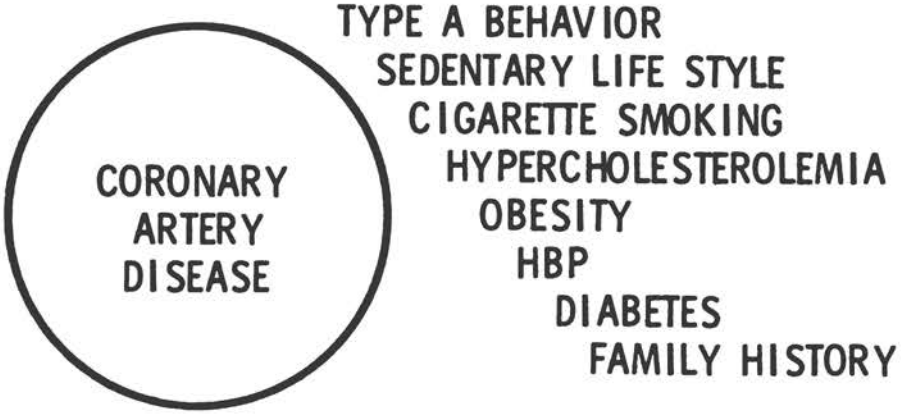


Figure 4. Risk factors for coronary artery disease.

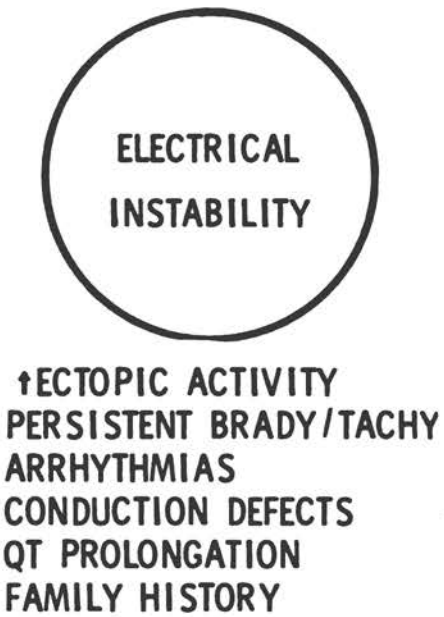


Figure 5. Risk factors for cardiac electrical stability.

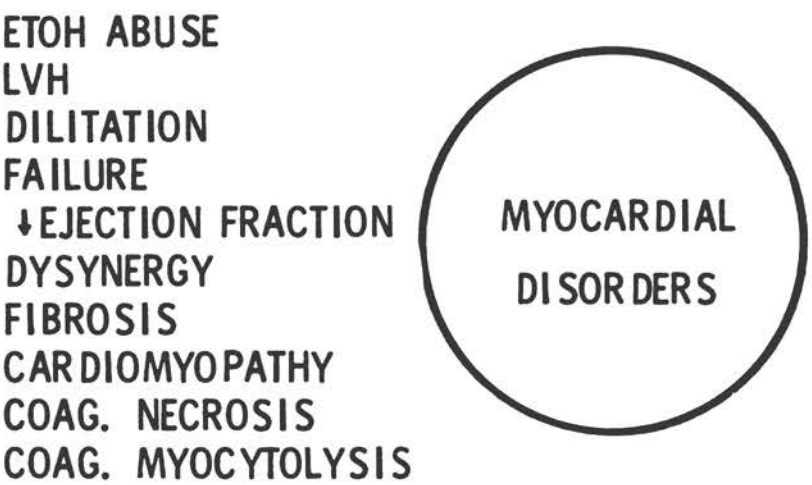


Figure 6. Factors associated with myocardial disorders

or more of the abnormalities listed: hypertrophy, dilation, clinical failure, depressed ejection fraction, dyssynergy, fibrosis, or global heart muscle dysfunction as in cardiomyopathy. If one has fibrosis, one must assume that there was an old inflammatory process, either coagulation necrosis, coagulative myocytolysis, myocarditis, or the like. In the realm of cardiomyopathy, a notable entity is idiopathic hypertrophic subaortic stenosis which has a high incidence of sudden death with or without coronary obstructive disease.

A fourth contributing factor (Figure 7) and the spearhead of this conference is that of biobehavioral modulators. Factors that have been incriminated in the process include Type A behavior, life crises, neuroticism, depression, and restricted coping options usually associated with low socioeconomic status. The central nervous system has long been thought to play an orchestrating role in the pathogenesis of the final event. Indeed, few folklore notions have enjoyed as widespread popularity as those that ascribe sudden death to emotional shock. The Bible tells us that when Ananias was charged by Peter, "You have not lied to man but to God", he fell down dead as did his wife, Sapphira, when told that "The feet of them which have buried thy husband are at the door and shall carry thee out" (Acts 5:3-10). Among physicians over the centuries, medical writings abound in accounts of collapse and death in the

midst of some emotional crisis. Everard Home's commentary on the demise of his brother-in-law, John Hunter, is but one example (Hunter, 1796). Physicians have long recognized the primacy of the central nervous system as a mediator and modulator of physiology. Until quite recently, however, any serious examination of the role of the central nervous system in sudden death has been discouraged by the dominance of single factor concepts of disease causation as well as the scientific bias toward cellular biochemical mechanisms.

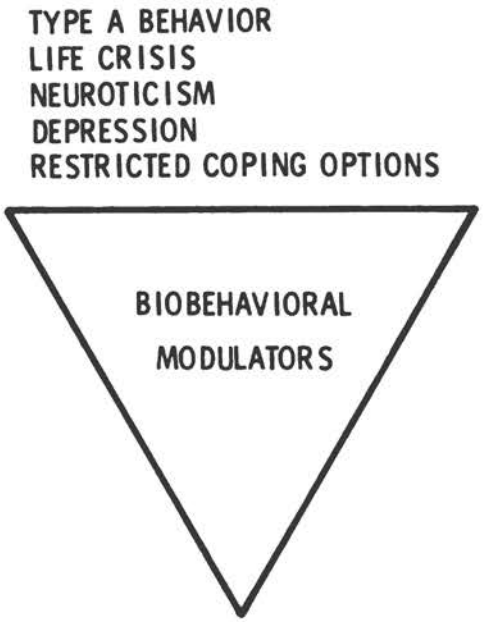


Figure 7. Biobehavioral modulators of CNS influence on cardiac function.

Yet today, the combined factors of age-old observations and scientific impetus in the cellular biochemical realm, such as the recent discovery of endorphins and enkephalins in placebo mechanisms, have renewed interest in the role of the central nervous system in sudden cardiac death.

A variety of studies suggest that psychosocial forces, behavioral factors, and the neuroendocrine system participate directly in the process of arrhythmogenesis. Myers and Dewar (1975), in studying the circumstances attending 100 sudden deaths with coroner's necropsies, found that the most significant relationship of sudden deaths was with acute psychological stress.

Moderate physical activity, the time of day, the day of the week, and a recent meal, especially if accompanied by alcohol, were also significantly related. Rahe and colleagues (1974) noted that an elevation in recent life change event data was particularly apparent in sudden death victims. Talbott, Kuller, Detre, and Perper (1977) noted in studies of sudden death in women that a history of psychiatric illness bore a definite relationship to sudden cardiac death. Educational incongruity, cigarette smoking, alcohol consumption, and less childbearing also tended to be risk factors. Evidence relating psychological stress to acute coronary events has been reviewed by Engel (1971,1976,1978), among others (Lynch et al, 1977; Lown et al, 1978). The enormous literature concerning psychosocial and behavioral factors and their relationship to cardiovascular disease is beyond the scope of this discussion except to point out that neurohumoral factors and behavior have been incriminated.

A broad overview of the candidate for sudden cardiac death may be depicted, therefore, as in Figure 8. The candidate for sudden cardiac death is seen as one approaching the center of these overlapping figures. Risk factors tend to increase one's likelihood of being incorporated into one or more of these figures of influence.

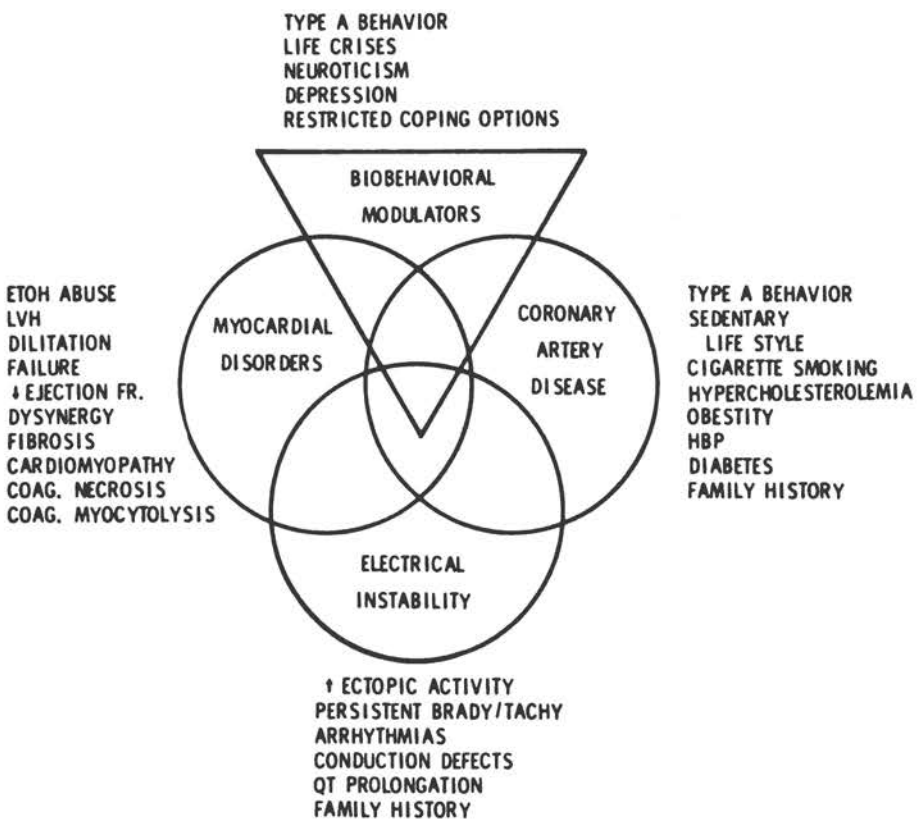


Figure 8. Risk factors for sudden cardiac death.

As with all the risk factors, it should be noted that the biobehavioral elements are not really just restricted to the area above the triangle, but tend to cascade down over coronary artery disease risk factors and other risk areas as well. Certainly alcohol abuse is a behavior, lifestyle is a behavior, smoking is a behavior, overeating is a behavior, and perhaps biobehavioral elements also impinge upon the electrical threshold as well.

A composite description of the sudden death victim falls within these boundaries as depicted. However, the most frequent presentation is that of a middle-aged man with either clinical or subclinical coronary disease. He is frequently hypertensive and/or diabetic and usually smokes and drinks to excess.

One can summarize the major focus of this conference by means of an overview of the pathophysiologic pathways involved in three major spheres of influence. Given the observation that sudden cardiac death almost always occurs in the abnormal heart without uniformly predictive antecedent histologic and/or clinical features, it is apparent that a mosaic of modifying and modulating factors must be invoked that work upon a vulnerable substrate (Figure 9). The

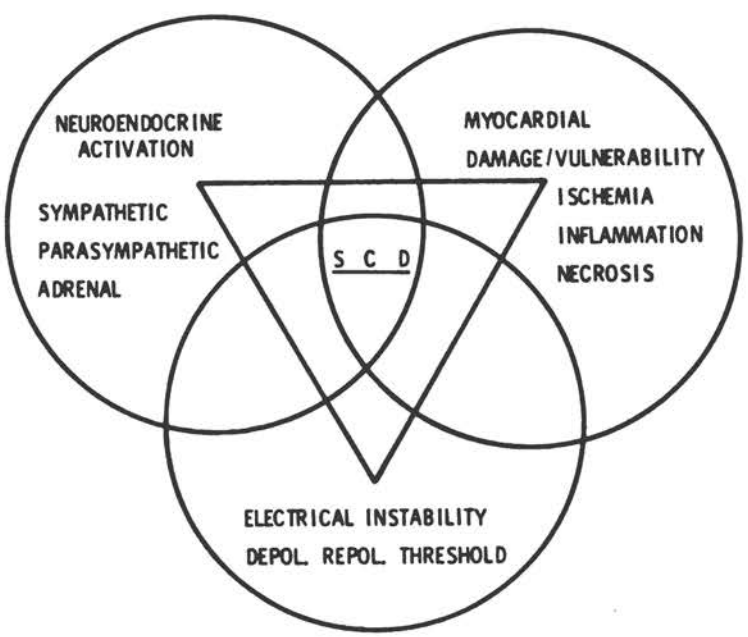


Figure 9. Pathophysiological pathways in sudden cardiac death.

triangle of sudden cardiac death appears to fit within spheres of myocardial damage/vulnerability, electrical instability, and neuroendocrine activation. Each side of the triangle represents a pathophysiological link between these spheres of influence. The link between myocardial damage/vulnerability and its creation of factors leading to electrical instability has been well studied and comprises a well known, enormous body of literature. Whether through ischemia or inflammation or necrosis, the resultant fibrosis, altered conduction velocities, dispersion of recovery periods, etc., are well appreciated mechanisms by people examining sudden death.

We would like to confine our comments to the other two sides of the triangle, namely mechanisms by which neuroendocrine activation influences both electrical instability and myocardial damage/vulnerability.

Arrhythmogenesis

Lethal arrhythmias have been provoked experimentally in animals by electrical stimulation of the brain and occur spontaneously in patients with subarachnoid or intracerebral hemorrhage (Connor, 1968; Burch et al, 1970). Lown and coworkers (1977b) have focused upon neural and psychologic mechanisms in the pathogenesis of sudden cardiac death. In their work, the primary emphasis is upon the ability of central nervous system stimulation to lower the ventricular threshold to repetitive ectopic activity and/or ventricular fibrillation (Axelrod et al, 1976; Blatt et al, 1977; Corbalan et al, 1976). The arrhythmogenic potential of central nervous system stimulation is not accompanied by hemodynamic alterations nor adrenal activity; although increased sympathetic activity, whether induced by neural or neurohumoral action, predisposes the heart to ventricular fibrillation. Protection is achieved with surgical or pharmacologic denervation or maneuvers that reduce sympathetic tone. Lown et al (1976b,1977b) have demonstrated in certain subjects that diverse stresses and various psychologic states provoke ventricular ectopic activity. Studies by Verrier et al (1975) revealed that the electrical threshold for ventricular fibrillation was significantly reduced by posterior hypothalamic stimulation. Approaching the problem from the other side, Rabinowitz and Lown (1978) increased central serotoninergic stores by injection of precursor and enzyme blockers since such a treatment has been shown to diminish sympathetic activity. This treatment produced significant increases in the threshold of the ventricle for repetitive extrasystoles after exogenous stimulation.

In animal studies, a stimulating electrode placed more rostrally to the region of the ventromedial nucleus did not precipitate arrhythmias during stimulation but did so after the stimulus was turned off (Evans and Gillis, 1978). During stimulation, heart rate and blood pressure increased; following cessation of stimulation, heart rate fell and nodal or ventricular heart beats were seen. This was due to a reflex cholinergic mechanism which could be blocked by anticholinergics, and if the stimulus bound hypertension was prevented either by hemorrhage or sympatholytics, so too was the arrhythmia. The ability of brain or sympathetic nerve stimulation to produce arrhythmias is increased when the heart is made ischemic, but apparently can also occur in hearts without coronary disease.

While Lown and coworkers have focused upon the sympathetic components of the autonomic nervous system and their arrhythmogenic potential, Engel (1978) has tended to emphasize vagally mediated factors in establishing the imbalance between sympathetic and parasympathetic systems. He has also emphasized the potential adverse effects of giving up in the face of emotional arousal and psychologic uncertainty. In support of this posture is the work of Kerzner et al (1973) showing that vagal stimulation in the ischemic heart also can precipitate ventricular tachycardia. The studies of Corley, Mauck, and Shiel (1975) in yoked monkeys and Gelhorn's (1967) observations between the two systems under severe stress tends to validate the potential contributions from this concept. Schneider (1957) observed that among patients who had a past myocardial infarction, those with the greatest tendency to bradycardia in response to startle also had the poorest prognosis. Indeed, according to Hinkle et al (1972), a constant slow heart rate in middle-aged men is a risk factor for sudden death.

Suffice it to say at this time that the mechanisms responsible for arrhythmic death appear to heavily involve disturbances of the central neural circuitry that regulates the heartbeat. The details of these underlying neural pathways and mechanisms are becoming better understood. Activation of the mechanisms may occur from central circuits which, in turn, have been stimulated by emotionally stressful circumstances as well as by afferent impulses originating from injured areas of the myocardium. Whereas brady- and tachyarrhythmias represent the electrophysiologic components and the final pathway to sudden death, other investigators have focused upon other neurohumorally mediated mechanisms as contributing factors.

Histologic Abnormalities

Sudden cardiac death is a rare event in histologically normal hearts and one of the most frequent histologic abnormalities found is that of coagulative myocytolysis. The fact that this form of necrosis, consisting of anomalous contraction bands as a characteristic feature, can be found in central nervous system lesions and produced by catecholamine injections, suggests that neurohumoral excess as well as the creation of metabolic imbalances render the myocardium more vulnerable to a final electrical catastrophe.

Following reports of a high incidence of sudden death at the Kennedy Space Center, Eliot and coworkers (1974) began to investigate the role of sympathetic arousal due to stress as an operating mechanism. Obvious evidence of the Kennedy Space Center personnel being under stress included the high incidence of alcoholism, divorce, drug abuse, and a highly ambiguous work environment (Warheit, 1974; Reynolds, 1974). With the exception of 1970, annual death rates from 1968 through 1974 showed that consistently larger percentages of Kennedy Space Center employees succumbed to acute cardiovascular death than the percentage of the total white male population of the state of Florida. Although traditional risk factors were not reported to be greater, psychoneuroticism was rampant and coagulative myocytolysis was found among the majority of those experiencing sudden unexpected cardiac death (Warheit, 1974; Eliot et al, 1977). This hyperfunctional form of necrosis has been well described in cases of pheochromocytoma and in association with a variety of examples of so-called stress-induced sudden death.

The results of beta-adrenergic administration to dogs showed a marked increase in left ventricular work (dP/dt) and significant reductions in the level of total high-energy phosphates with preferential depletion of the inner layer (Eliot et al, 1978; Pieper et al, 1979a, 1979b). As compared to coronary artery ligation, the metabolic derangements from catecholamine administration were found to be similar, although contractility was increased by catecholamine administration and decreased during coronary artery ligation (Eliot et al, 1978; Pieper et al, 1979b). In addition to mimicking the contraction band lesions of coagulative myocytolysis, these studies also point toward severe mechanical overdrive as a fundamental factor in contraction band formation because these lesions occur in large numbers only following isoproterenol infusion (Eliot et al, 1977,1978). The metabolic, histologic, and hemodynamic abnormalities of isoproterenol infusion could be largely ameliorated by beta blockade (Eliot et al, 1978; Pieper et al, 1979a). The favorable response to beta blocking agents in the prevention of sudden death in clinical studies, together with the histologic

similarity between sudden cardiac death and catecholamine administration, suggests that neurohumoral mechanisms may likely participate in the pathogenesis. A well documented link between psychosocial perturbations and dramatic neurohumoral responses is well known and requires no further comment in suggesting linkages between coagulative myocytolysis and central nervous system function. A variety of psychosocial stress studies in various animal models point to the very real association between emotion, behavior, and pathophysiologic responses.

Other Mechanisms

The association between clinical depression and corticosteroid excesses as a prominent "stress" indicator (Francis, 1979), the high incidence of atherosclerotic sequelae in Cushing's Syndrome, and the correlation between depression and coronary heart disease suggest that sympathetic nervous system and adrenal medullary excesses are but part of the relationship between the neurohumoral system and sudden cardiac death.

As pathophysiologic mechanisms, coronary artery vasospasm and thrombotic mechanisms are somewhat removed from the immediate electrical event. Coronary spasm was a suspected mechanism at the turn of the century, but because it was undetectable at the necropsy table, it was largely ignored as a pertinent mechanism until coronary arteriography could document its existence. Now work by a variety of investigators has demonstrated changing coronary arterial tone in unstable angina, exertional angina, acute myocardial infarction, and sudden death (Conti and Curry, 1980). The coronary vessels are richly innervated and coronary spasm can certainly be induced by adrenergic nerve stimulation in the normal coronary arterial bed of the dog (Hillis and Braunwald, 1978). Because coronary tone can be increased by alpha adrenergic receptor stimulation and phenoxybenzamine can block the reflex coronary vasoconstriction regularly elicited by the cold pressor test, another neurogenic mechanism appears capable of participating in the pathophysiology of sudden death (Mudge et al, 1976a).

The interrelationship between coronary spasm and platelet function has also gained new emphasis. When circulating platelets are aggregated by thrombin or as a consequence of endothelial injury, thromboxane A2, a powerful local coronary arterial vasoconstrictor, can be synthesized and released (Needleman et al, 1977). Indeed, Alexander et al (1978) have regularly characterized the alpha adrenergic receptors on human platelets. A variety of studies have demonstrated abbreviated clotting times, enhanced platelet aggregation, and "hypercoagulability" attending a variety of stress responses. Folts et al (1976) demonstrated a reduction in coronary flow following ligation in dogs which could be blocked by

pretreatment with aspirin; this suggested that platelet microaggregation somehow participated in coronary flow reduction. In addition to participating in the sequelae of atherosclerosis, the recent finding of platelet derived growth factor and its ability to induce smooth cell proliferation suggests that stress mechanisms may also participate at more fundamental levels of the atherosclerotic process (Kaplan, 1979). The variety of potentially atherogenic mechanisms which may be fostered or produced by catecholamine and/or corticosteroid excesses is beyond the scope of this paper except to mention that the neuroendocrine system likely participates at multiple levels in the evolution of a process culminating in sudden cardiac death.

Physicians and physiologists alike have long recognized the importance of the central nervous system in the modification and modulation of a variety of organ systems and physiologic responses. The orchestration of the autonomic nervous system has long been known to be under central control, and now, with the advent of newer technologies, a variety of previously described endocrine hormones are found to have neurotransmission functions with the central nervous system. It seems teleologically fitting, if not fully understood scientifically, that the operations and functions of each organ might interact with a central monitoring system to insure that each plays in harmony with the whole.

Sudden cardiac death accounts for some 450,000 deaths annually with the vast majority succumbing to ventricular fibrillation with little or no warning and no evidence of acute myocardial infarction. The usual findings at autopsy consist of acute coagulative myocytolysis engrafted upon the ravages of chronic coronary atherosclerosis or other chronic myocardial disease processes.

In summary, then, it is hoped that Figure 9 will provide a helpful frame of reference in approaching this problem. As this conference proceeds, each investigator will inflate one or more of these balloons with experience and insight based upon personal perspective, interest, and expertise. In the end, to the degree we understand these interrelationships, we will better understand and recognize the clinical and pathophysiologic factors culminating in the phenomenon of sudden cardiac death.

OVERVIEW OF THE EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH AND ITS BEHAVIORAL ANTECEDENTS

C. David Jenkins, Ph.D.

Sudden cardiac death has been known since antiquity and was held in awe during those ancient times because it was rare and mysterious. It forms the basis for this conference because it has now become epidemic in industrialized countries (Lown, 1979), while still remaining inadequately understood.

It is estimated that between 300,000 and 450,000 sudden non-traumatic deaths occur in the United States each year with the great majority being cardiac crises in adults (Weinberg, 1978; DeSilva and Lown, 1978a). The incidence of sudden cardiac death in the United States is quite similar to that observed in the British Commonwealth and in Scandinavia. In general, the epidemiology of sudden cardiac death (SCD) closely parallels that of mortality for arteriosclerotic heart disease (ASHD), with some intriguing deviations which will be noted later.

Before proceeding to a more detailed exposition of the epidemiology of SCD, let me point out that attempts to summarize the scientific literature are fraught with difficulty despite -- or perhaps because of -- a substantial number of research studies which have been reported. The first problem encountered is the widely varying definition of sudden cardiac death (Kuller et al, 1966; Weinberg, 1978). Most published studies define SCD as unexpected death within 24 hours of onset of acute symptoms, in a normally functioning person free of symptoms of acute disease prior to the final episode, and for whom other causes of death cannot be discerned (Kuller et al, 1975; Baroldi et al, 1979). Other studies, while retaining the criterion of prior normal functioning, restrict sudden cardiac deaths to those dying within one hour of the onset of symptoms (Doyle et al, 1976; Cobb et al, 1980a). A few studies have included all cardiac deaths occurring within 28 days of onset of symptoms. The published studies of SCD also differ with regard to the rigor with which they attempt to exclude other causes of sudden demise, some relying on detailed autopsy findings for definition of the cases, but others being satisfied with witnesses' reports of the events surrounding the fatal episode. Some studies excluded persons with recent myocardial infarction or other current clinical manifestations of coronary artery disease from their samples (Baroldi et al, 1979).

Many studies of sudden death limit themselves to coronary death, while others broaden their criteria to include all forms of cardiac death. Where careful pathological series have been obtained, one finds that perhaps as many as 85-90 percent of sudden cardiac deaths are in fact sudden coronary deaths. Furthermore, it is important to recognize that among the studies purportedly limiting themselves to sudden coronary deaths, those with less stringent exclusionary criteria and those with lower autopsy rates may be more nearly approximating a cardiac death series rather than a coronary death series.

At this stage of epidemiologic data collection, there is no clear evidence of major discrepancies in the broad outlines of the social characteristics of the epidemiology of sudden coronary death as contrasted with sudden cardiac death, largely because of the overlap of the two entities.

Needless to say, this lack of comparability of the definition of sudden death and the criteria for exclusion of persons from the case group lead to quite different collections of clinical data. This introduces spurious heterogeneity into the results reported. If common factors emerge from such disparate samples, however, they should lend confidence to the importance of the finding which has been observed by the consensus.

Another problem in reviewing epidemiological and large-scale clinical studies of SCD has been the relatively limited focus of most such studies. Some reports are based only on autopsy series and have no clinical data. Still others have clinical data, but no pathological findings; and still a third group may report coronary risk factors and demographic variables, but fail to cover clinical or pathological findings on these same cases.

Despite these problems in assembling a coherent consensus of findings from the published literature, the reviewer has been impressed by the large number of carefully conducted, large-scale investigations into the phenomenon of SCD. Many of the summary statements to be offered will rest heavily on a few of the larger, more comprehensive studies and collections of papers.

Incidence of Sudden Cardiac Death

Most published studies of SCD are based on convenience samples or sequential series from a hospital or a coroner's office. In the 1960's and 1970's, however, there were a number of population studies based on death registries from geographic areas, usually large cities. The World Health Organization has taken leadership in enlisting a number of cities in Europe in a common protocol for the

Table 1

Annual Incidence of Sudden Cardiac Death per 1000 Population

For Males by Age

Population	Ages	30-39	40-49	50-59	60-69	70-79
Edinburgh, Scotland[1] Armstrong et al, 1972 (cited in Fraser, 1978)		---	1.2	3.2	5.7	---
Auckland, N.Z.[2] Fraser, 1978		0.3	0.7	4.2	7.2	---
Helsinki, Finland[3] Romo and Ruosteenoja, 1978		0.2	1.3	3.1	5.9	12.3
Oslo, Norway Holme et al, 1980		---	0.7	---	---	---
	Ages	35-44	45-54	55-64	65-74	
Nashville, USA[3] Hagstrom et al, 1971 Cited in Fraser, 1978		0.5	1.3	4.8	---	
Albany, USA[4] Kannel et al, 1975		---	0.9	4.1	1.9	
Framingham, USA[4] Kannel et al, 1975		---	1.5	3.6	3.2	
Baltimore, USA[3] Kuller, et al, 1975						
WHITE		---	2.2	4.5	---	
BLACK		---	2.0	3.6	---	

1. Medically Unattended Deaths Presumed to be SCD.
2. Death within 24 hours in ambulatory persons with symptoms consistent with cardiac cause, other criteria also.
3. Deaths within 24 hours.
4. Deaths within 1 hour in apparently well persons, with other cause of death suggested by medical history.

Table 2

Annual Incidence of Sudden Cardiac Death per 1000 Population

For Females by Age

Population	Ages	30-39	40-49	50-59	60-69	70-79
Edinburgh, Scotland[1] Armstrong et al, 1972 (cited in Fraser, 1978)		---	0.0	0.6	2.2	---
Auckland, N.Z.[2] Fraser, 1978		---	0.3	0.6	2.2	---
Helsinki, Finland[3] Romo and Ruosteenoja, 1978		---	0.1	0.5	0.9	2.1
Oslo, Norway Holme et al, 1980		---	---	---	---	---

	Ages	35-44	45-54	55-64	
Nashville, USA[3] Hagstrom et al, 1971 Cited in Fraser, 1978		0.1	0.4	1.5	
Albany, USA[4] Kannel et al, 1975		---	---	---	
Framingham, USA[4] Kannel et al, 1975		---	---	---	
Baltimore, USA[3] Kuller, et al, 1975					
	WHITE	---	0.5	1.0	
	BLACK	---	0.4	1.2	---

1. Medically Unattended Deaths Presumed to be SCD.
2. Death within 24 hours in ambulatory persons with symptoms consistent with cardiac cause, other criteria also.
3. Deaths within 24 hours.
4. Deaths within 1 hour in apparently well persons, with other cause of death suggested by medical history.

study of myocardial infarction and sudden death (Furberg et al , 1977). These WHO population registries provide the most comprehensive knowledge we have of incidence of SCD and its clinical and pathological correlates. The autopsy rates in these European cities often exceed 90 percent in contrast to United States studies where the autopsy rate has ranged from about 50 percent to as low as six percent.

Pathological studies are extremely important in verifying cause of death. Particularly among the many sudden deaths occurring outside of a hospital, death certificates and even clinical judgments of attending physicians are often seriously in error. The extent of this problem is exemplified by a study conducted at Lund University in Sweden, which collected a series of 100 sudden deaths in adults having no suspicion of unnatural cause, no evidence of trauma, and no hospitalization immediately prior to death (Lundberg and Voight, 1979). Complete autopsies on this series revealed that only 49 of these 100 cases could be attributed to coronary artery disease, and eight to other cardiac causes. The remaining cases -- nearly half of the total -- were attributable to 19 other medical conditions. It is true that most clinical and epidemiological studies of SCD reviewed in this paper were based on more stringent criteria for ASHD which would have excluded many of these other causes. It is equally true, however, that a sizeable fraction of the sudden deaths would not have been excluded from the SCD category without post-morten examination. Thus, it is appropriate to caution that the validity of studies of sudden and unexpected death is roughly proportional to the autopsy rate within the study group.

The mortality rate due to cardiac diseases increased throughout the 20th century with only brief deviations from a steady upward climb. This continued until about 1968 to 1970 in the United States, from which time a marked decrease in coronary mortality, now approaching 20 percent, has been observed (Kannel and Thom, 1979). The decade of decline shows no sign of termination. Although evidence is less firm for SCD than it is for total cardiovascular disease mortality, it is very probable that SCD mortality has also decreased proportionately since the mid-60's (Kuller et al, 1975). There is no evidence that the sex ratio of sudden coronary deaths may have changed, and recent data is lacking on the distribution of durations of the fatal episode, the latter information having implications regarding the pathological mechanisms involved in SCD. From the limited amount of comparison data available, there is no reason to suspect other aspects of the epidemiology of SCD have also changed along with the decline in incidence rates (Kuller et al, 1975). Nevertheless, this review will concentrate on those epidemiologic studies of SCD which have been conducted during the decade of the 1970's in the interest of presenting a more timely picture.

From the larger number of competently conducted, population-based epidemiologic studies of the incidence of sudden cardiac death completed during the 1970's, we have selected eight which represent populations from different parts of the world. Despite the different ethnic backgrounds, climates, eating and smoking habits, patterns of physical activity and other aspects of lifestyle, the incidence rates by age and sex are remarkably similar. Studies from Edinburgh, Scotland; Auckland, New Zealand; Helsinki, Finland; Oslo, Norway; and four United States studies (Nashville, Albany, Framingham, and Baltimore) agree rather closely in their observations of SCD rates rising from about 0.2 per thousand for males ages 30-39 to about six per thousand at ages 60-69 (see Table 1, which also cites the respective references). The degree of female protection from sudden cardiac death is equivalent to 15 years of age. That is, women age 60 have approximately the same SCD rates as men age 45 (see Tables 1 and 2).

Although the rate of SCD continues to rise in populations at least to about age 80 in Europe, a paradox is noted in that the proportion of all ASHD deaths which are sudden deaths is highest in persons below age 50, and thereafter begins to decline as a proportion of total ASHD deaths (Romo and Ruosteenoja, 1978). Researchers drawing inferences only from ASHD death data report a decrease in the percentages of such deaths which are SCD after age 50, but a decline in incidence is not observed when the denominator for the rate is the total living population rather than the total number of ASHD deaths. One exception to this is that in Albany and Framingham, a decline in the population incidence of SCD was noted in men ages 65 to 74 compared with men one decade younger (Kannel et al, 1975). This has not been observed in other population based studies. The apparent reason for the decline in SCD as a proportion of total cardiac deaths is the fact that other forms of less abrupt cardiac mortality are increasing at a much faster rate than sudden cardiac death in those age cohorts where chronic, progressive cardiac decompensation is very common.

Another of the remarkably consistent features of the epidemiology of sudden cardiac death in urban industrialized areas is the ratio of male to female SCD incidence rates in populations. In all countries studied, males have a far greater risk of SCD by anywhere from a two to one, to a five to one ratio when age is not considered. In a study in Helsinki where male/female ratios in incidence of SCD were calculated for each decade of age, males under age 50 had 11 times the female rate, in the next three decades had six times the female rate, and only after age 80 did the ratio narrow to 3 to 1 (Romo and Ruosteenoja, 1978). The sex distributions of sudden cardiac death in populations and several autopsy series are shown in Table 3.

Table 3
Sex Distribution of Sudden Cardiac Death
In Populations and Pathology Series

Locale	% Male
Auckland, N. Z. (Fraser, 1978)	76%
Oxford, England (Kinlen, 1973)	80%
Milan, Italy (Baroldi et al, 1979)	87%
Helsinki, Finland (Romo & Ruosteenoja 1978)	75%
Edinburgh, Scotland (Armstrong et al, 1972)	78%
Denmark (Bekker & Grunfeld, 1975) (Cited in Ostergaard, 1966)	66%
Baltimore (Blacks) (Kuller et al, 1966)	64%
Baltimore (Whites) (Kuller et al, 1966)	79%

An important aspect of sudden cardiac death is the duration of the fatal episode. The speed of death has been studied by many researchers in the expectation that it might assist in sorting out the several mechanisms which may be involved in sudden demise. Results from several such studies are shown in Table 4.

Table 4

Distribution of Duration of Fatal Episode
for Cardiac Deaths before 24 hours
(Cumulative Percent Mortality)

Limits of Time Intervals	Milan[1]	Helsinki[2]		Oxford[3]	Scandinavia[4]		Newcastle[5] Upon-Tyne	San Francisco[6]
		Men	Women		Men	Women	Men	
Ten minutes or less								
One hour	95%	—	—	78%	65%	51%	73%	57%
Two hours	—	88%	81%	—	—	—	—	—
Three hours	100%	—	—	88%	—	—	—	—
24 hours	Excluded	100%	100%	100%	100%	100%	100%	100%

1. Baroldi et al, 1979
2. Rissanen, et al, 1978
3. Kinlen, 1973
4. Romo and Ruosteenoja, 1978
5. Myers and Dewar, 1975
6. Friedman et al, 1975

The general thrust of these studies, as well as of others with less detailed data, is that half or more of cardiac deaths occurring within 24 hours to apparently healthy persons will occur in the first ten minutes of the critical episode. By one hour, about two-thirds to three-fourths of the full day's death toll has already been exacted. These findings have implications for the amount of SCD reduction which an ambulance program can provide to a community (Cobb et al, 1980a).

The speed of demise in SCD differs between men and women, with a higher proportion of men dying within the first ten minutes.

Comparison of the clinical and pathological features of persons dying within one hour with those dying later in the first 24 hours generally reveal rather little in the way of differences, except of course, that most pathology methods are less able to detect evolving myocardial infarctions having very short durations before death.

The distinction between sudden death and instantaneous death (i.e., within about a minute), as emphasized in the writings of Meyer Friedman in particular, is much more rewarding in terms of discovering clinical and pathological differences (Friedman et al, 1973). Autopsy studies of cases of instantaneous death rarely reveal fresh thrombi or fresh infarctions. The cause of death is almost certainly ventricular fibrillation. These deaths account for a particularly high proportion of SCD in young men and often occur during or immediately after unusually heavy exercise (Friedman et al, 1973; Kala et al, 1978). Recent studies of young athletes dying suddenly included a high preponderance of instantaneous deaths, and in autopsies where particular attention was paid to the phenomenon, myocardial over-bridging of arteries, particularly the left anterior descending, was often discovered (Maron et al, 1980; Cheitlin, 1980). In older cases of instantaneous death, advanced coronary atherosclerosis is generally found in much the same proportions as for other non-instantaneous sudden deaths.

The epidemiology and pathology of instantaneous cardiac deaths seem to differ in important aspects from that of other sudden deaths, and this category should be treated separately and examined more intensively in future epidemiologic studies.

Biological, Behavioral, and Psychosocial Risk Indicators for Sudden Cardiac Death

Another approach to unraveling the etiologies of SCD is through searching for its risk indicators and contrasting these with the risk factors for acute myocardial infarction. There have been two approaches to this work: (1) contrasting SCD cases with the general population, and (2) contrasting them with non-fatal or less immediately fatal acute myocardial infarction cases.

Comparisons of SCD cases with the general population reveal a series of risk indicators which is quite similar to those possessed by future myocardial infarction and angina pectoris patients. Arguing from these risk indicator studies alone, one might infer that SCD is merely one presentation of atherosclerotic heart disease.

Comparisons between risk indicators for SCD and those for non-fatal myocardial infarction present a somewhat different picture. Representative studies of this type are displayed in Table 5. Heavy smoking is a consistent risk factor for SCD. Sudden death cases tend to include higher proportions of smokers, particularly heavy smokers, as compared to non-fatal MI groups -- who in turn are more likely to be smokers than the general age-sex matched population (Kannel et al, 1975; Fraser, 1978). In most studies, hypertension has been more common in SCD than in MI cases. Excessive alcohol abuse has been reported as a risk factor for SCD (but not for myocardial infarction) in New Zealand (Fraser, 1978), and Sweden (Wilhelmson et al, 1973). Obesity, lack of exercise and serum cholesterol tend not to be distinguishing factors between SCD and MI cases. The generally negative findings with regard to serum lipids as conferring added risk for SCD suggest that given an advanced level of lipid-facilitated atherosclerosis, this factor has no further participation in the specific mechanism of sudden death.

Table 5

Risk Factors Significantly More Frequent in SCD than Non Fatal MI in Selected Studies

Study Locale	Heavy Cigarette Smoking	Hypertension	Obesity	Lack of Exercise	Low SES	Psychologic Stress
Auckland (Fraser, 1978)	+		0		+	
Helsinki (Rissanen et al, 1978)	+	+				+
Scandinavia (Furberg et al, 1977)	+	+	0	0	0	
Newcastle upon Tyne (Myers & Dewar, 1975)	0	0	-	0	+	+
New York Weinblatt et al, 1978)	0	0			+	
San Francisco (Friedman et al, 1973)	+	0	+	+/-		

Blank entry indicates variable not evaluated
+ indicates positive association
- indicates negative association
0 indicates no association

Table 5 also reveals two psychosocial risk indicators which distinguish SCD from AMI (acute myocardial infarction) cases. Sudden death cases are more likely to come from lower socioeconomic status than the average non-fatal infarction case (Myers and Dewar, 1975; Fraser, 1978; Weinblatt et al, 1978). They also have been found to have undergone acute psychological stress more frequently in those studies where a specific effort was made to elicit this information (Myers and Dewar, 1975; Dimsdale, 1977; Engel, 1978; Rissanen et al, 1978a; Siltanen, 1978; Cottington et al, 1980).

Women less frequently have severe atherosclerosis and sudden death than men. Recent work in Baltimore has shown female SCD victims to be more often divorced and single and to have a history of psychiatric treatment than matched controls (Kuller et al, 1975).

These findings were replicated in western Pennsylvania, where it was also found that women who died suddenly had fewer children (among the married), and less education than their spouses (among the married). All SCD women as a group consumed more alcohol and were more likely to have experienced the death of a close friend or relative in the past six months than had matched controls (Talbott et al, 1977). The SCD women did not have other categories of life crises with greater frequency, however (Cottington et al, 1980).

Animal research by Lown and others have shown the importance of neural mechanisms in precipitating ventricular arrhythmias and fibrillation (Bergamschi and Longoni, 1973; Verrier and Lown, 1978c; Lown, 1979). These experimental findings make the epidemiologic observations of psychological stress as a possible acute precipitating risk factor for SCD seem quite plausible.

A few studies have considered the situational concomitants of SCD. Some of these have considered season of the year; time of day; whether the person was at work, at home, exercising, or resting. These variables have not been regarded consistently enough by epidemiologists to provide a basis for confident generalizations. One study of time of day of SCD suggests the highest risk to occur during daytime hours from 6 a.m. to 6 p.m. (Fraser, 1978). Another such study implicates the evening, 6 p.m. to 10 p.m. (Myers and Dewar, 1975). The first hour or two after a meal also appear to be at higher risk (Myers and Dewar, 1975). It is notable, however, that of the several studies addressing time of day of fatal episode, none have found the highest rates to occur during the usual period of sleep from 10 p.m. to 6 a.m. Sleep has been found to be a period having a paucity of arrhythmic activity (Lown et al, 1973a). This is in contrast to studies of acute myocardial infarction where the sleeping hours are as prominent times of attack as any others (Myers and Dewar, 1975).

In terms of place of the attack, the few studies which have examined this carefully tend to find a paucity of SCD occurring while people are on the job. Home, recreation, or daytime casual activities are much more common circumstances for SCD (Kinlen, 1973; Fraser, 1978). Of the days of the week -- a characteristic seldom reported -- Saturday was by far the most common time for SCD in the series studies by Myers and Dewar (1975). The cooler months of the year may be the highest risk season (West, 1976; Fraser, 1978), but this was not confirmed in Scandinavia (Furberg et al, 1977).

The issue of the role of strenuous exercise in precipitating sudden death is extremely controversial. Most studies speaking to this issue are based on small and often biased clinical series. My intuitive summary of the variety of data which has been included in the epidemiologic literature is that a fairly strong case has been made for heavy or unusual exercise as a risk factor for precipitating instantaneous cardiac death, but that there is no such evidence that it increases risk of those episodes which last from 15 minutes to 24 hours before demise (Friedman et al, 1973; Myers and Dewar, 1975; Kala et al, 1978).

Prodromal Symptoms

The analysis of signs and symptoms preceding the terminal event in SCD has potential value both in understanding the mechanisms of the phenomenon and in facilitating emergency care and prevention of the fatal event. Study of prodromal symptoms has been common in clinically oriented studies but generally lacking in pathologically oriented research.

There are important methodological problems in obtaining data on prodromal symptoms which need to be mentioned, if only briefly. Such studies usually depend on the reports of family members or witnesses to the fatal event. Methodological studies, such as those by Gillum et al (1976) have shown that next of kin systematically over-report some prodromal symptoms and under-report others. In cases of non-fatal MI, where comparison can be made with the report of the surviving patient, the question can then be raised as to which report is more valid. Many patients with coronary heart disease have been found to be deniers of their symptoms as well as the seriousness of their disease (Gentry, 1979). To the extent that this is true, they would tend to under-report such symptoms as chest pain or fatigue when asked by an interviewer, but they would also refrain from complaining of these symptoms to family members, thus reducing the value of that source of information. On the other hand, symptoms and signs which are externally observable, such as fatigue-induced reduction of activity or shortness of breath, might be more reliably reported by a close companion than by the patient. These are difficult problems which may not be completely

resolvable. Yet an upgrading of common research practice can be achieved. For example, one pitfall which should be avoided is drawing inferences about the differences between fatal and non-fatal arrhythmias on the basis of contrasting reports from next of kin with reports of surviving patients; this difference in source of information must certainly lead to substantial bias.

Given these caveats, there are still valuable lessons to be learned from the many good studies which have concerned themselves with prodromal symptoms (Nixon and Bethell, 1974; Feinleib et al, 1975). A review of such data is presented in Table 6. Chest pain, fatigue, and dyspnea are the most commonly studied symptoms and hence the most commonly reported. Where gastrointestinal symptoms and sleep problems were also systematically inquired about, they turned out to be quite common.

It is not surprising to note that changes in angina and in some cases the beginnings of chest pain are very commonly found in the days and weeks immediately preceding SCD. In general, about one-third to one-half of SCD cases report such symptoms to their families. Intense and unusual fatigue is an even more common

Table 6

Prodromal Symptoms in the Month Preceding Sudden Coronary Death

		Percentage of Cases with Symptom				
Site of Study	(N.)	Angina/ Chest Pain	Fatigue	Dyspnea	"Indigestion" Nausea	Sleep Problems
Baltimore, MD (1)						
Males	(--)	35	63	52	29	33
Females	(--)	37	53	60	40	43
Montgomery (2) County, Md	(88)	35	42	39	17	--
Helsinki, Finland (3)	(118)	53	38	18	5	--
Auckland, N. Z. (4)						
Males	(134)	31	46	20	--	--
Females	(42)	41	39	32	--	--
Oxford, England (5)	(142)	33	41	--	--	--
Milan, Italy (6)	(84)	57	--	35	--	--
Framingham, MA (7)	(19)	32	68	21	--	--
San Francisco, CA (8)	(64)	11	13	5	--	--

(1) Kuller, 1978
(2) Alonzo et al, 1975
(3) Rissanen et al, 1978
(4) Fraser, 1978
(5) Kinlen, 1969 (cited in Feinleib et al, 1975)
(6) Baroldi et al, 1979
(7) Gillum et al, 1975 (cited in Feinleib et al, 1975)
(8) Friedman et al, 1973

prodrome to sudden death (Alonzo et al, 1975; Kuller, 1978). In the eight studies which systematically reported both symptoms, fatigue was more common than chest pain in six of the studies (see Table 6 for references). The subjectivity of such studies was a cause for concern for some of the critical researchers. Several report, however, that when exploring these symptoms in a non-directive fashion, they received anecdotes of extreme and unusual fatigue -- surprising to both patient and family -- such as falling asleep in the middle of a meal or suddenly giving up long-time favorite activities because of lack of energy. Shortness of breath was also commonly reported to have begun or to have become aggravated in the month preceding SCD (Alonzo et al, 1975).

Inasmuch as all these symptoms are quite non-specific and common in the general population, they cannot be readily used as a screening technique for identifying persons as at elevated immediate risk of SCD. It should be possible, however, by use of careful psychometric procedures to develop standardized methods for administering multi-item scales which would be much more sensitive in distinguishing those truly at elevated risk of SCD from those with more general and less dangerous collections of symptoms. Indeed, the beginnings of such research are already under way in the form of the Maastricht questionnaire. This questionnaire dealing with exhaustion and emotional drain has been found to distinguish significantly between groups of patients with recent myocardial infarction and other sick and well groups (Appels et al, 1979).

It would be valuable to study the pathophysiologic mechanisms which can generate angina, fatigue, dyspnea, and related symptoms and fit them more neatly and with greater understanding into the chain of events which lead to sudden coronary death. Even though these symptoms may be epiphenomena rather than participate directly in the causal sequence, they nevertheless may provide the signals which, when taken in proper pathophysiological context, would alert physicians to performing appropriate medical or laboratory studies which would more sensitively separate persons with high and low risk of impending SCD. A preliminary approach to such a conceptual framework is offered later in this paper.

Social and Behavioral Factors

To what pathophysiologic processes in the etiology of sudden coronary death do social and behavioral factors contribute? How great is their impact on each of these mechanisms? Combining them, what is their overall role?

A complete answer to these questions awaits a more definitive understanding of the natural history of the antecedents of sudden

coronary death and the pathophysiology of the mechanisms involved. Even now, however, it seems to this observer that a wide variety of social, psychological, and behavioral characteristics are significantly intertwined with most of the known mechanisms involved in sudden coronary death. Figure 1 presents a preliminary schema which seeks to lay out graphically some of the known relationships and to make more explicit a series of hypotheses, both concerning the mechanisms of sudden coronary death and the involvement of behavioral factors in the process.

Figure 1, although extremely complex (some might consider it merely confused), undoubtedly underestimates the true complexity and multiple interactions of overt behavior, psychological response, physiological process, and transient or irreversible pathology.

It will be noted that it stratifies variables into those observable at the social level, the psychological-behavioral level, the biological level, and then considers contributing pathology, both physiological and anatomical, in increasing levels of proximity to the final end point, sudden cardiac death. Careful consideration of extant research literature documenting the involvement of social with psychological variables and each of these in turn to such biological risk factors as low density serum lipids, obesity, and hypertension, demonstrates the importance of social and behavioral factors as influences on standard risk factors for atherosclerotic heart disease. In addition, many behavioral risk factors have documented associations directly with obstructive coronary atherosclerosis, myocardial infarction, and future development of angina pectoris.

Not only do behavioral factors raise the risk of sudden cardiac death through their influence on arteriosclerotic heart disease, but in addition may influence the risk of cardiomyopathy, such as through the association of excessive alcohol usage with congestive cardiomyopathy. In addition, alcohol usage appears to have a direct influence on the electrical stability of the myocardium. Numerous clinical and laboratory research studies have shown the relation of anxiety and other strong emotions to acute changes in blood pressure, blood clotting, and blood platelet aggregation.

In persons with intramural coronary arteries ("bridging") excessive strenuous exercise may precipitate sudden death, and other behaviors may interact deleteriously in persons with mitral valve prolapse or other structural anomalies (Maron et al, 1980). Acute stress has been reported to precipitate exacerbations of congestive heart failure (Perlman et al, 1971).

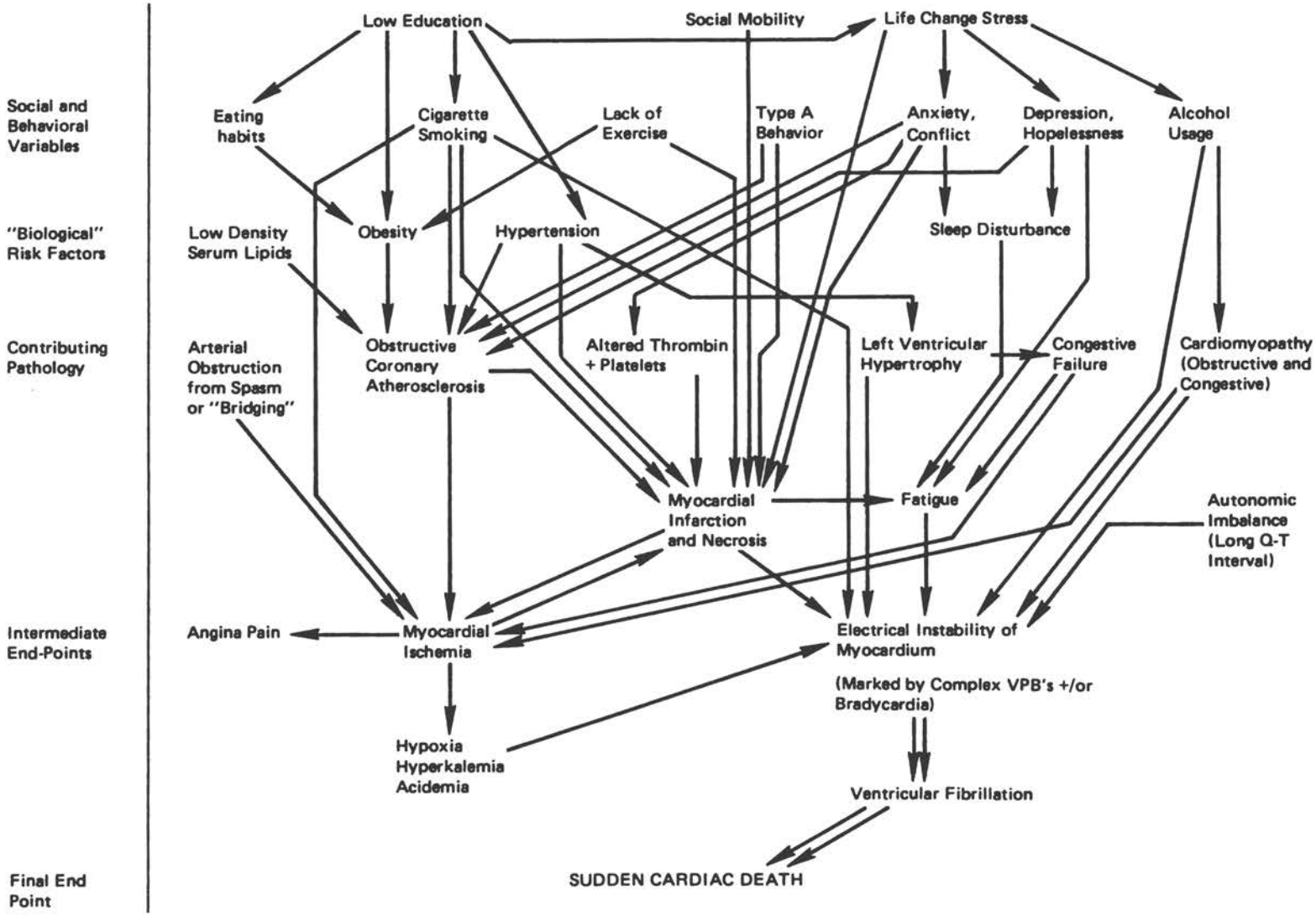


FIGURE 1 Possible Links Between Social and Behavioral Factors, Cardiovascular Pathology, and Risk of Sudden Coronary Death

Additional evidence for the impact of emotional responses on several pathologies contributing to risk of sudden cardiac death can be adduced from the known relation of stress, anxiety, anger, and hopelessness on autonomic nervous function and catecholamine excretion (Dimsdale, 1977; Lown et al, 1977b; Engel, 1978). The role of the autonomic nervous system and epinephrine and norepinephrine on such cardiovascular parameters as heart rate, myocardial oxygen demand, vagal and sympathetic tone, vasodilation and constriction, and irritation of arterial intima have all been well documented. Several studies have presented more direct evidence of the involvement of social, behavioral, and emotional variables in SCD. These are discussed and cited earlier.

Let us trace the possible impact of one social variable, low education, on risks of sudden coronary death. It has been observed in epidemiologic studies that persons having low education have different eating habits that those with high education. The diet of the individual with a low level of education is more likely to be comprised of a higher percentage of carbohydrates and fats, and this raises the level of low density serum lipids and contributes to obesity. Studies have also shown that the ideal body image of persons in lower socioeconomic status (also mostly of low education) calls for a more heavy and rounded figure as compared to the preference of higher SES persons for a slim body image. Recent surveys also show that persons of low education are more likely to be heavy cigarette smokers than those of high education. In addition, the U.S. National Health and Nutrition Examination Survey has revealed strong association of low education and low occupational levels with elevated blood pressures and hypertension. Elevated serum lipids, obesity, cigarette smoking, and hypertension all raise the risk of obstructive coronary atherosclerosis. Obesity also raises the risk of hypertension and together they increase the probability of left ventricular hypertrophy, which is a direct risk factor for electical instability of the myocardium and sudden cardiac death. In addition, persons of low education have been found to experience more life change stress in the form of losses and painful experiences than persons who are better educated and in a higher social class (Dohrenwend, 1973). Life change stress has in some research (mostly retrospective) been associated with higher risk of myocardial infarction (Siltanen, 1978), but other reports support this finding only for the circumstance of very severe losses (Cottington et al, 1980). Life change stress also seems to raise the probabilities of anxiety, chronic conflict, depression, hopelessness, and excessive alcohol usage, at least on a temporary basis. Each of these in turn has an impact on such intermediate risk factors as sleep disturbance, fatigue, and atherosclerotic deposition, thus raising the probabilities of myocardial infarction or, even in its absence, having an apparent direct role as a precipitating risk factor in electrical instability of the

myocardium and its resultant arrhythmias which may lead to ventricular fibrillation and sudden cardiac death.

Each entry in Figure 1 could be examined similarly in terms of already published research linking it in a network with many other variables involved in SCD.

Figure 1 is offered not as a blueprint for how sudden cardiac death comes to pass, but rather as a basis for discussion and controversy, which in turn might generate testable hypotheses and research plans. The main messages of this conceptual framework in its current preliminary state are as follows:

1. Sudden cardiac death has a variety of antecedents with most caseshaving Arteriosclerotic heart disease (ASHD) as the primary contributor, but a significant minority seemingly primarily determined by cardiomyopathy, structural anomalies and residua of previous diseases.

2. There are many contributing causes to electrical instability of the myocardium, and very often it requires a combination of such causes to generate a lethal arrhythmia. Some examples would include an acute anxiety state occurring in a fatigued person whose myocardium has been compromised by fibrotic scars from past myocardial infarctions, or unusually active exercise in a person with obstructed coronary arteries as a result of Type A behavior and cigarette smoking.

3. Social conditions impact on a variety of behavioral and emotional responses and these in turn can enter the matrix of cardiac pathology at a wide variety of places. Thus, many behavioral factors may contribute risk through many alternate pathophysiologic pathways which combine in different ways in different individuals to heighten the probabilities of sudden cardiac death, either by promoting predisposing pathology or by participating in a final triggering event.

Summary and Implications

Sudden cardiac death is a major social and public health problem in the United States and in all industrialized nations. It is extremely difficult to study scientifically because of the technical problems of retrospective study of sudden fatal events. This raises technical problems for pathologists and clinicians as well as for physiologists, epidemiologists, and behavioral scientists. The ideal study from a technical point of view would be prospective, but in view of the tremendous sample sizes required and the resulting

increase in research costs, such an approach would not be feasible unless it was set up as a by-product of a larger comprehensive longitudinal study conducted for other purposes.

Considerable research is already published concerning many aspects of sudden cardiac death. This research is deficient in that most such studies focus only on limited aspects of the phenomenon (e.g., the pathology) and thus fail to have either a broad enough time perspective, or a multi-disciplinary approach. Most research into sudden death has in past decades been conducted under quite varied and frequently non-comparable research protocols. The recent initiative by the World Health Organization to set up myocardial infarction and sudden death registries in many large European cities, all using a common protocol, provides us with the most comprehensive, comparable, and extensive data on sudden death. In the United States, the National Institutes of Health should strongly encourage use of a common protocol as the core for data collection in U.S. studies of this phenomenon.

The published epidemiologic studies on sudden cardiac death provide a remarkably consistent description of the basics regarding high risk populations, the distribution of rapidity of the fatal event, some ideas regarding risk factors and prodromal symptoms, and documentation at the experimental, clinical, and epidemiological levels of the involvement of a wide variety of biological, social, behavioral, and emotional factors at all stages of the development and emergence of SCD.

Already efforts to predict SCD using an array of clinical cardiological predictors are achieving acceptable sensitiviey (Moss, 1975). Oxman was able to identify 95 percent of future SCD cases among a pool of carefully evaluated patients (Oxman et al, 1973). Oberman's group has also developed a promising system (Oberman et al, 1975). The major problem of these equations is the excessive rate of false positives, which unduly alarms many people who do not actually carry such high risk. The addition of more specific variables to these equations, perhaps including psychosocial, behavioral, and prodromal variables might improve prediction equations substantially.

Finally, a broad perspective on the involvement of social and behavioral factors in sudden coronary death needs to be synthesized not only from studies focused on sudden death itself, but also from related research on cardiovascular conditions and mechanisms implicated in the many pathways through which risk of sudden death may be elevated. Such a broad perspective will reveal that social, behavioral, and emotional factors impact on many different cardiovascular and central nervous system processes which are of documented importance in determining risk of sudden cardiac death.

CLINICAL OBSERVATIONS ON THE PSYCHOBIOLOGY OF LIFE-THREATENING ARRHYTHMIAS

Peter Reich, M.D.

My vantage point on the problem of sudden death has been as a psychiatrist working with Dr. Bernard Lown and his group on the management of patients with life-threatening ventricular arrhythmias. In the past five years, we have seen over 150 of these patients, more than half of whom had survived out-of-hospital cardiac arrest.

Having worked in the same hospital for more than 20 years, I can appreciate the impact of this problem. Only a few years ago, we rarely saw such survivors. Now there may be as many as four or five in the hospital at one time. As the effectiveness of rescue programs grows, this new population of patients will increase still further. They are highly vulnerable to recurrences, and so for them the question of whether sudden cardiac death can be precipitated by behavioral factors has an immediate personal relevance.

I plan to review some of the clinical evidence associating acute psychological events with sudden death. There are surprisingly few systematic studies in this area, even though such observations might contribute to the understanding of basic pathophysiological processes. I will start with an illustrative case from our own series.

A 56-year-old professor with no history of heart disease was visiting his family home at Christmas when he suffered a cardiac arrest. While visiting the same city at Christmastime two years previously, his wife had died suddenly and was buried in the family plot. He had not been back since then. For several weeks prior to the visit, he had been thinking about death and even redid his will. He chose to sleep in the same room where he had spent the night after his wife's death and planned to visit her grave for the first time the next morning. After breakfast he felt restless and went out to shoot some baskets in the back yard. He was joined by his nephew and later by his brother, who suggested that they play a game. The professor paused briefly to rest and collapsed. He was in ventricular fibrillation (VF) when the rescue team arrived. After resuscitation there was no evolution of a myocardial infarction and subsequent angiography revealed minimal coronary disease. He has done well for over three years since that time.

This patient was mildly depressed for several weeks, although he functioned adequately at work, and was in an agitated anticipatory state just prior to his near fatal arrhythmia. He had slept poorly the night before and was engaging in moderate exercise. In addition, he was suffering from an anniversary reaction of his wife's death. All of these elements joined to form a unique situation. The association of these elements with a unique cardiac event in the absence of serious heart disease is suggestive of a causal link.

Similar anecdotes describing patients who died during fright, anger, despair, or at times of extreme stress are common in the literature on sudden death. Some of these case reports give well-documented evidence of repeated associations between arrhythmias and intense emotions; for example, Wellens' (1972) report of a 13-year-old girl with long QT syndrome who had ventricular fibrillation in association with loud noises, and our report of a 39-year-old educator with normal coronaries who had VF twice during emotional stress (Lown et al, 1976b).

In 1971, George Engel described 170 newspaper reports of people who died suddenly after intense experiences associated with events such as death of a loved one, personal danger, loss of status, and, occasionally, success or a happy reunion (Engel, 1971). Some of these deaths occurred hours or days after the events occurred. For example, a 69-year-old man was driving back from the grave of his wife who had been buried the day before when he had a minor car accident. While a policeman was finishing his report, the man walked around, got back in his car, and slumped over dead. In another example, a 53-year-old physician became enraged when his chief, who was retiring, told him he would not be promoted to the chiefship. Four days later he saw the chief again, and then a few hours after that was seen to be angry and died suddenly with VF noted on the cardiogram.

These examples raise the question that goes through this entire clinical review: Why now? What is the relationship between the instantaneous event, the acute arrhythmia, and the behavioral states that were ongoing when the arrhythmia occurred. Presumably the physician had three times when he might have died suddenly, given the underlying condition of his heart and the fact that he was experiencing anger and shock. Why did he die after the third episode of anger?

Engel pointed out the need for more precise documentation of the events preceding sudden death and also called for epidemiological studies to determine the frequency with which sudden death is associated with intense experiences.

Greene, Goldstein, and Moss (1972) reported one of the first studies that dealt with the issue of the frequency of this association. They described 26 sudden deaths in a population of 44,000 employees of the Kodak Company. Through information provided by spouses and others they concluded that at least half of the patients had been depressed for weeks or months before death and then had died suddenly during acute arousal, increased activity, anxiety, or anger. For example, a man who was depressed by his son's antisocial behavior died suddenly when he became angry after his son was caught stealing again. Another man, aged 66, who had been depressed over the illness of his wife and daughter, died suddenly after winning an intense billiard game. The authors also noted that in half the cases there were no indications of unusual psychological states preceding death.

Two more recent studies have looked at psychological and behavioral precursors of sudden death in larger samples. In Table 1 these studies are compared to our series.

Table 1

ACUTE STRESS AND SUDDEN CARDIAC DEATH

	Population (Data Source)	Series	M:F	Average Age (Range)	Time Frame	Patients Under Stress
Myers, Dewar (1975)	Coroner's records (observers)	100	100:0	57.4 (35-70)	30 min.	23
Rissanen, Romo, Siltanen	Urban deaths (observers)	118	94-24	57.1 (31-83)	12 hr.	23
Reich, DeSilva, Lown, Murawski (1981)	Referrals (Patients)	117	90:27	52.4 (17-79)	24 hr.	25

In the first study, Meyers and Dewar (1975) reconstructed the circumstances preceding sudden death in 100 cases identified through coroners' records in Newcastle upon Tyne. Through information provided by relatives and friends, they looked for evidence of emotional stress and other behavioral factors, including exercise, eating, smoking and drinking during the day of the fatal episode, and then compared these cases to 100 patients who had suffered

nonfatal myocardial infarcts. They found evidence of acute psychological stress during the last 30 minutes of life in 23 of the sudden death victims. In comparison, only eight of the myocardial infarction patients were under stress in the 30 minutes before the onset of symptoms. Of the other variables, only moderate exercise and recent meal consumption correlated with sudden death. In addition, 40 of the sudden death victims and 24 of the MI patients appeared to be suffering from chronic or subacute stress as well. Examples of acute stress preceding sudden death were cystoscopy, attack by dogs, a row over a dominoes game, a road accident, and a divorce notification.

In a similar study of 118 sudden death victims in Helsinki, Rissanen, Romo, and Siltanen (1978a, 1978b) found evidence of acute stress of less than 12 hours' duration before death in 30 cases. With the exception of one instance that was described as sudden fright, the stresses themselves were only described in general terms such as distress, excitement, and exceptional physical exercise.

In our series, of the 117 patients first reported, we found evidence of acute emotional distress preceding arrhythmias in 25 (Reich et al, 1981). We had the advantage of being able to interview living patients who could describe their subjective experiences in detail. We also had corroborative information from relatives. In the remaining 92 patients, we found no evidence of emotional stress during the 24 hours preceding arrhythmias.

These three studies form a remarkably consistent picture, even though their methods and populations differed. In each, only a fraction of the patients, approximately 20 percent, seemed to have experienced unusual stress during the day of the fatal or potentially fatal episode. The comparison is Newcastle upon Tyne, 23 percent; Helsinki, 19 percent; and Boston, 21 percent. Whether this trend will hold up in more thorough epidemiological studies remains to be seen. Conceivably, a subpopulation of patients can be identified who tend to develop arrhythmias in response to psychological disturbances. This possibility is in line with the concept which states that individuals have different patterns of reaction to stress and thus develop psychosomatic disorders along lines of preexisting patterns and vulnerabilities.

If a subset of patients who develop arrhythmias after psychological disturbances can be identified, it might follow that these patients differ physiologically or psychologically from other patients with arrhythmias. The Newcastle upon Tyne and Helsinki studies did not address this question; we made some preliminary observations that tended to confirm this possibility.

Table 2 displays all the patients in our series of 117 in terms of underlying heart disease, as determined clinically, and their

most serious grade of arrhythmia. In all instances, the arrhythmias were not associated with acute myocardial infarction (AMI). The predominant number of cases had coronary artery disease. Other heart diseases included cardiomyopathies, hypertensive disease, rheumatic heart disease, and mitral valve prolapse. We had an unusually large group of patients who suffered life-threatening arrhythmias without any evidence of structural heart disease at all. In most series of sudden death victims, this latter group of patients with no apparent structural disease is less than five percent.

Table 2

DISTRIBUTION OF PATIENTS WITH VENTRICULAR TACHYCARDIA AND FIBRILLATION AS A FUNCTION OF UNDERLYING HEART DISEASE

	Ventricular Fibrillation	Ventricular Tachycardia with Syncope	Ventricular Tachycardia	Total	Average Age (Range)
Coronary artery disease	44	8	24	76	57.9 (25-79)
Other heart disease	9	2	9	20	47.3 (17-75)
No demonstrable heart disease	9	3	9	21	37.4 (17-64)
Total	62	13	42	117	52.4 (17-79)

Table 3 shows the 25 patients who reported acute psychological disturbances prior to arrhythmias. They include a disproportionate number of patients with no demonstrable heart disease. Several of the patients with coronary heart disease had relatively little arterial involvement on angiography. When compared to the rest of the series, significantly more of the patients with psychological disturbances had VF and ventricular tachycardia (VT) with syncope, the more severe arrhythmias. These differences in the profile of heart disease and severity of arrhythmia were significant at $p < 0.005$, suggesting that patients who develop arrhythmias in the presence of psychological stress may have more severe arrhythmias with less serious structural heart disease.

Table 3

DISTRIBUTION OF PATIENTS WITH VENTRICULAR TACHYCARDIA AND FIBRILLATION WITH ANTECEDENT PSYCHOLOGICAL DISTURBANCES AS A FUNCTION OF HEART DISEASE

	Ventricular Fibrillation	Ventricular Tachycardia with Syncope	Ventricular Tachycardia	Total	Average Age (Range)
Coronary artery disease	8	3	1	12	55.3 (35-67)
Other heart disease	2	0	0	2	45 (39-51)
No demonstrable heart disease	6	3	2	11	37.9 (25-50)
Total	16	6	3	25	46.9 (25-67)

We gave all our patients psychological tests, and each was interviewed by myself. The tests did not differentiate the patients with psychological disturbances from the others, nor could I say with assurance that there were consistent differences in personality style or emotional conflicts between the two groups. Overall, the patients in the series were a heterogeneous group with respect to psychological variables.

If there is a psychosomatic vulnerability, it might be revealed by a psychophysiological approach. An effective psychological stress test that could help determine whether a patient develops arrhythmias during psychological stress would be a powerful tool. Another approach would be the search for biochemical markers, such as the response of beta adrenergic receptor sites in white cells or levels of catecholamines and catecholamine metabolites in serum immediately prior to the development of arrhythmias.

A major concern of studies in this area is the need for adequate controls. It seems highly unlikely that the intercept of a unique psychological event and a unique cardiac event is a random occurrence. For example, the statistical probability of an event such as the devastating failure of a family business and the only occurrence of ventricular fibrillation in a 39-year-old man with normal coronaries, as in one of our cases, seems remote. Nevertheless, it would be important to know how many people in the general population are experiencing emotional disturbances on any given day. If this figure approaches 20 percent, it would call into question the association between psychological events and

arrhythmias in 20 percent of patients who die suddenly. Beyond this general control group, it seems logical to use patients as their own controls by determining whether arrhythmias occur randomly in their lives or whether they are associated with unusual periods of emotional disturbance. The studies reported so far should be viewed as preliminary. There is clearly the need for more systematic approaches.

By far the most frequent emotion seen in our patients prior to arrhythmias was anger. Seventeen of the 25 patients experienced anger in some form, often mixed with fear. For example, a man developed ventricular tachycardia whenever he had violent angry impulses to hurt his wife. Other affects included despair, fear, and, in one instance, high excitement over an impending victory. In the literature, anger, arousal, and activation are the consistent picture of the affective states associated with arrhythmias and sudden death.

In our series, psychological disturbances seemed to interact with other behavioral states in an additive way. For example, a woman had a cardiac arrest after staying up all night feverishly securing her house against an impending hurricane. Later, when safe and exhausted, the attack occurred. A man who habitually jogged had a cardiac arrest while jogging after an extremely upsetting fight with his wife. He had another episode while jogging after a long hazardous drive through a storm with his daughter at the wheel. He was in excellent condition and jogged every day. Sometimes a strong emotion would lead to an arrhythmia and sometimes it would not. For example, a man I knew well became angry at the cardiac team and was about to complain when he developed rapid VT. Another man became enraged at me after reading a note I had written in his chart. He had previously developed serious arrhythmias while angry. He raged at me for 20 minutes while I mentally practiced cardiopulmonary resuscitation, but he seemed fine throughout.

It is also important to consider the circumstances preceding death in the 92 patients who were not experiencing unusual emotions when their attacks occurred. For example a 53-year-old man was hitting a few tennis shots, waiting for two partners to arrive, after a routine day and an early supper with his wife, when he collapsed in VF. We investigated his situation very carefully and found no evidence of emotional disturbance. In another case, a young woman who was waiting to be seated at the Harvard Club after a day of sightseeing was being greeted by an old friend when she had a cardiac arrest. More information is needed on the circumstances of these patients who develop life-threatening arrhythmias with no apparent behavioral precipitants.

Subacute emotional states, particularly depression and agitation, have also been implicated as precursors to sudden cardiac

death, although the data on this association are more difficult to evaluate. In both the Newcastle upon Tyne and the Helsinki studies there was evidence suggesting that more sudden death victims were suffering from chronic stress than might be expected. In a recent epidemiological study of sudden cardiac death in women in Alleghany County, Pennsylvania, it was found that sudden death victims were six times more likely to have experienced the death of a significant other within the previous six months than matched controls, suggesting that the emotional and behavioral state associated with bereavement increased vulnerability to fatal arrhythmias (Cottington et al, 1980). This carefully designed study gives confirmation to previous, more impressionistic observations of an association between bereavement and sudden death. These findings need to be translated into the emotional experiences of the patient. Without psychological data it cannot be assumed that depression is the pathogenic state associated with bereavement. Depressing issues are all too common in the midlife years when sudden death has its peak, and depression itself has such a high prevalence in the general public that it seems unlikely that depression alone can account for an increased incidence of sudden death.

Nevertheless, the weight of evidence associating depression with sudden death or with poor prognosis after AMI is impressive, and we have noted that many of the patients in our series had been depressed for weeks or months prior to their near fatal arrhythmic episodes. The depressions we have seen in these patients were usually mixed with agitation and tension. A number of our patients were preoccupied, brooding, disappointed, and bitter. They were suffering from insomnia and physical tension. This type of depression is in contrast to the sad, passive, depleted depressions often seen in older patients or in patients with medical illnesses. For example, a man who had been cheated in business by his own brother was so obsessed, disillusioned, and bitter that he felt the experience had poisoned his whole personal life. He could find no relief from this state. It persisted for several months prior to an episode of VF. Another man had been injured at work and was preoccupied with gloomy thoughts of compensation and revenge when he had severe VT. In a third case, a retired man had repeated episodes of VT when thrown into grim daily struggles with his chronically dissatisfied wife who constantly reproached him for his inadequacies and repeatedly threatened to leave him. Clearly more systematic data are needed before an association between these depressive states and sudden death can be assumed.

At an even more speculative level, we have been impressed by subgroups of patients in our series with long-standing personality traits in common. There was a group of unusually hyperactive, forceful young women who had recurrent VT. There also were an unusual large number of athletic, aggressive, and hyperactive men. When large series of sudden death survivors become available, it would be worth while to look at personality traits more carefully.

It is hard to summarize the heterogeneous clinical data available so far on the possibility that sudden cardiac death has emotional precursors. It would be premature to reduce the complexity of these observations to generalities at this point. At best, clinical observations cannot establish a causal link between emotions and arrhythmias. Experimental work utilizing animal models, psychological stress tests, and neurochemical approaches are promising, but the experimentalists should keep the clinical complexity in mind and not develop models that are out of touch with this reality.

In considering psychobehavioral data, it is useful to distinguish between subacute and acute states or events. Examples of the former would include depression, sleep deprivation, or fatigue, and of the latter would be sudden fright, rage, or a physical act. In our experience there were relatively few arrhythmias that appeared to be precipitated by brief psychological states of a few minutes' duration. The occasional arrhythmia that is associated with a massive shock or a sudden surge of anger or fear seems quite rare. More often, intense psychological states of 30 minutes or more duration were associated with arrhythmias. The implications of these observations for the neurophysiological and biochemical mechanisms are worth considering.

My experience with this series of patients leads me to comment briefly on the problem of brain damage among survivors of sudden cardiac death. It has been demonstrated that any patient who has suffered total cessation of blood flow to the brain may sustain brain damage, even though the interruption of flow seems to be brief. The concept of a critical threshold of time is difficult to apply to the clinical situation where many variables operate and where it may not be possible to ascertain precisely how much anoxia the brain has sustained.

To my knowledge, the prevalence of mild brain damage marked by personality changes and emotional problems rather than by changes in formal mental status <u>per se</u> has not been studied systematically among these patients. If personality changes occur and control over impulses and affect are impaired, the biobehavioral and neurophysiological situation with respect to the heart may be altered. These changes may bear on the problem of prevention of recurrence in survivors.

The statistics on survival after resuscitation, even when the best resuscitation programs are available, are still quite poor. Survival and quality of life are largely limited by the state of the central nervous system after cardiac arrest. For example, in one report, only 15 of 117 patients admitted to a hospital after cardiac arrest were found to be neurologically normal upon discharge (Earnest et al, 1979). Many of the more subtle changes associated

with minimal brain damage are not apparent on discharge and are missed by standard psychological tests and mental status examinations. They may not appear until the patient tries to reenter a job situation or social milieu. Often only the spouse sees the personality changes that may include loss of interest, lack of empathy, poor judgment, loss of sense of humor, and mild evidence of loss of emotional control (Lezak, 1978). These symptoms may be mistaken for emotional reactions to the experience of illness.

I have seen four patients who had personality changes after cardiac arrest that resulted in divorce in three cases and loss of job in the other. These changes were thought to be purely emotional initially and only later when the possibility of brain damage was entertained were subtle changes identified on psychological testing and mental status examination.

I have also seen the relief experienced by the patient and by the family when the problems are recognized as stemming from mild brain damage rather than from emotional disturbance. Simply knowing that these personality changes are physical and are to a large extent not under the control of the patient makes the clinical situation easier to bear for all concerned.

Finally, I want to make some general comments on the contributions psychiatrists can make to the care of patients with life-threatening arrhythmias. Although the role of biobehavioral factors in the pathogenesis of arrhythmias is not clearly established, attention to the life situation of each patient has contributed to the management of the cases in our series. We need to assess whether psychotherapy or psychoactive drugs can help in the prevention of recurrences.

In our experience the spouses of patients who have survived sudden death have often needed psychiatric attention. For example, several wives were in serious anxiety states when their husbands arrived at the hospital. We have noticed the adverse effects of breakdowns in marital relationships on patients with vulnerability to arrhythmias. The maintenance of the family unit during stress may be another important preventive measure.

At times I am the most skeptical member of the team when the significance of psychological factors is being considered. Perhaps another role for a psychiatrist in the sudden death problem is to temper the enthusiasm of those who emphasize the importance of psychobiological factors.

EXPERIMENTAL STUDIES OF PSYCHOPHYSIOLOGIC FACTORS IN SUDDEN CARDIAC DEATH

Richard L. Verrier, Ph.D.

The exact relation between emotional states and the precipitation of fatal cardiac arrhythmias has eluded meaningful documentation. This has been due largely to the fact that until recently the occurrence of ventricular fibrillation (VF), the mechanism of sudden cardiac death (Lown, 1973), was an event of inescapable finality. As a result of widespread community instruction in cardiopulmonary resuscitation and the introduction of direct current defibrillation and cardioversion, increasing numbers of patients experiencing sudden death are being successfully resuscitated and are available for study (Schaffer and Cobb, 1975). While emerging clinical data and those of previous investigators (Engel, 1971; Lown et al, 1977b; Schwartz et al, 1978) point to a strong association between psychophysiologic variables and the genesis of malignant ventricular arrhythmias in man, the proof of causality will be difficult to establish incontrovertibly. Animal investigations will necessarily continue as a source of significant insights into the fundamental mechanism involved. The objectives of the presentation are (1) to summarize briefly what laboratory studies have taught us about the relationship between psychophysiologic factors and sudden cardiac death, and (2) to point out gaps in our present state of knowledge.

Early evidence of a link between higher nervous activity and cardiac arrhythmias was derived mainly from anesthetized animal experiments. Levy (1913) demonstrated over 60 years ago that injection of drugs such as nicotine, barium chloride, or epinephrine into certain areas of the brain in cloroform-anesthetized cats provoked major ventricular arrhythmias even when the coronary circulation was intact. The neural pathways involved in arrhythmogenesis were subsequently defined more precisely by electrical stimulation of various central nervous system structures by means of stereotaxically positioned electrodes (Korteweg et al, 1957; Hoff et al, 1963). Despite reasonable progress in anesthetized animal experimentation, advances in the psychologic dimension were few and far between.

The classic studies of Cannon (1942) suggested that the biologically active amine adrenaline was secreted in response to

stimuli that produced fear and rage reactions in animals, and he considered these biogenic amines to play a role in Voodoo death. Subsequently, the experiments of Richter (1957) exerted a profound influence in shifting the attention of psychologic investigations from the sympatho-adrenal system to the vagus as a precipitating element in sudden death. Richter demonstrated that rats forced to swim in water tanks died in bradycardia and asystole rather than from VF, presumably as a result of intense vagal discharge. While the simple faint in humans is caused by this means, this is unlikely to be the mechanism for sudden cardiac death in humans for two main reasons. First, whereas enhanced vagal activity is capable of permanently arresting the small rat heart, it is incapable of doing so in the larger mammalian hearts of the dog and humans (Mac William, 1887). Second, VF, not asystole, is the primary mechanism for sudden cardiac death (Lown, 1973).

Subsequent studies were directed toward exposing normal animals to severe behavioral stress until the animals either died or exhibited signs of extensive cardiac damage. These stresses involved interference of animals' access to food, or exposing rats to tape recordings of noisy rat-cat fights (Raab et al, 1964; Raab, 1966), and "yoked chair" aversive avoidance experiments in monkeys (Corley et al, 1975). Animal crowding was another stress situation imposed by Raab (1966). Subjecting normal pigs to unavoidable small electric shocks while they were paralyzed by muscle relaxants likewise induced cardiac myofibrillar damage with 24 hours (Johansson et al, 1974).

Thus, until recently (Table 1), psychophysiological studies in the area of sudden death research were oriented largely toward the provocation of myocardial injury and asystole in normal animals. This was an unfortunate trend because major features of the clinical syndrome which already were evident from coronary care unit experience in the 1960s (Lown et al, 1969) were ignored in designing biological models. For example, sudden death usually occurs in the presence of underlying coronary disease, not in normal individuals.

TABLE 1 - HISTORICAL PERSPECTIVE OF EXPERIMENTAL MODELLING OF BIO-BEHAVIORAL FACTORS IN SUDDEN CARDIAC DEATH

INVESTIGATORS	PERIOD	BIOLOGICAL MODEL	PROPOSED MECHANISM OF DEATH
CANNON	1942	"VOODOO DEATH"	SYMPATHO-ADRENAL ACTIVATION
RICHTER	1957	SWIMMING RATS	VAGALLY-INDUCED ASYSTOLE
RAAB	1964	SENSORY AND EMOTIONAL STRESS IN RATS	CARDIAC MYOFIBRILLAR DAMAGE
CORLEY	1974	SHOCK AVOIDANCE IN SQUIRREL MONKEYS	MYOCARDIAL DEGENERATION LEADING TO ASYSTOLE
JOHANSSON	1974	RESTRAINT STRESS IN PIGS	MYOCARDIAL NECROSIS

The products of many research efforts have produced a number of parameters which now have commonly been accepted as being characteristic of SCD. Among these characteristics are that the fatal event is usually abrupt in onset (symptoms lasting seconds to minutes) and that it is due primarily to VF, not asystole. Finally, significant myocardial damage is rarely present, suggesting that sudden death is due to a derangement in cardiac electrical function rather than to an anatomical lesion (Table 2).

TABLE 2 - CHARACTERISTICS OF SUDDEN CARDIAC DEATH SYNDROME

MECHANISM	ELECTRICAL FAILURE (VF)
DURATION OF FINAL EVENT	SECONDS TO MINUTES
CORONARY ARTERY DISEASE	PRESENT
ACUTE CORONARY OCCLUSION	ABSENT
MYOCARDIAL DAMAGE (ECG, ENZYMES, ETC.)	ABSENT

Thus, it was necessary to shift the research focus toward defining the influence of psychologic factors on ventricular electrical stability. This, however, presented difficult methodologic problems. Specifically, how can we assess vulnerability to VF in the free-moving conscious animal? Such assessment requires the use of painful test stimuli, induction of VF, and use of traumatic resuscitation procedures that preclude meaningful investigation of psychologic variables.

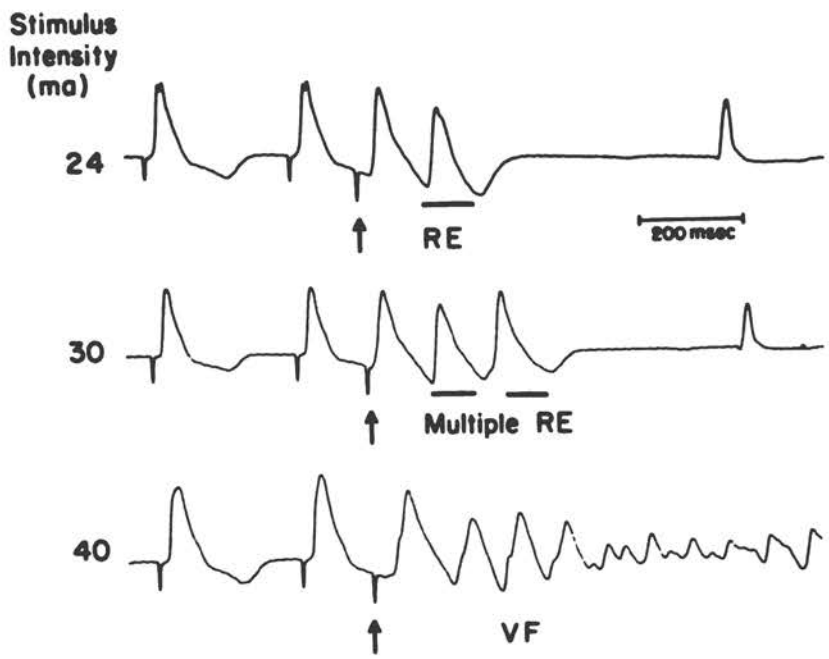
Assessment of Cardiac Vulnerability in Conscious Animals

To circumvent these difficulties, we utilized a different marker of ventricular vulnerability (Lown and Verrier, 1976a; Matta et al, 1976a). Classically, the threshold for ventricular fibrillation has been assessed by delivering small electric currents to the heart during the narrow zone of the so-called vulnerable period of the ventricle, coinciding with the apex of the T wave in the surface electrocardiogram. By stepwise increases of current intensity, ventricular fibrillation can be provoked and the electrical

threshold for this event measured. Since ventricular fibrillation is preceded by repetitive extrasystoles, the threshold for the latter endpoint may be utilized, because since it is not detected by the animal (Figure 1). This marker, which reliably tracks the threshold current required to provoke ventricular fibrillation, acts as a surrogate for the ventricular fibrillation threshold and obviates the need for cardiac resuscitation.

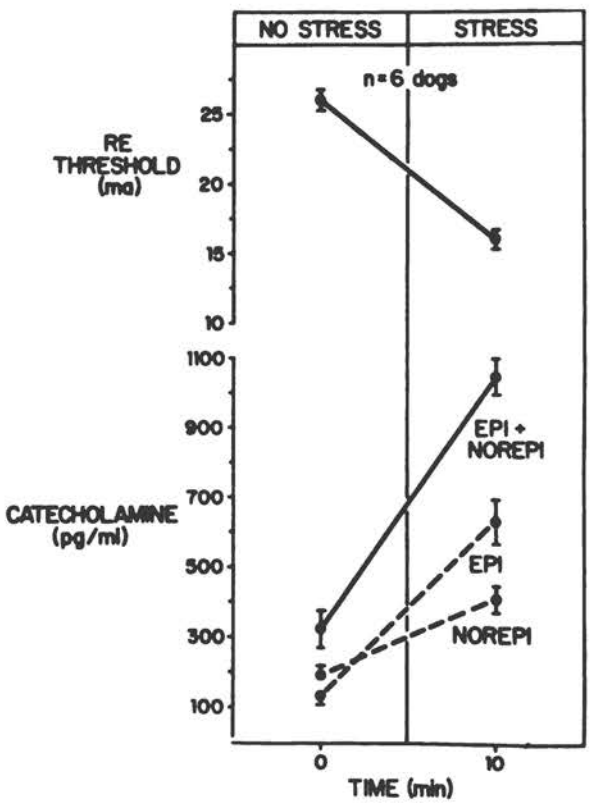
Psychologic Influences on Ventricular Vulnerability

The repetitive extrasystole therefore served as our essential electrophysiologic endpoint for examining the effects of diverse psychologic states on cardiac vulnerability. In our initial studies



(Figure 1) Repetitive responses preceding ventricular fibrillation (VF). At a stimulus intensity of 24 mA (arrow), a repetitive extrasystole (RE) is elicited (upper panel). At 30 mA, multiple RE ensue (middle panel) that degenerated into VF when stimulus intensity was raised to 40 mA (lower panel). Heart rate was maintained constant at 214 beats/minute by pacing. Tracings are intracavity ECGs recorded at 125 mm/sec. (From Matta et al., 1976a, with permission.)

a simple classical aversive conditioning protocol was utilized (Lown et al, 1973b). Dogs were exposed to two different environments: a cage in which the animal was left largely undisturbed and a Pavlovian sling in which the animal received a single five joule transthoracic shock at the end of each experimental period for three successive days. The two environments were compared on days four and five. At these times, dogs in the sling were restless, frequently salivated excessively, exhibited somatic tremor, demonstrated sinus tachycardia, and had increased mean arterial blood pressure. In the cage, the animals appeared relaxed as evidenced by behavioral signs and hemodynamic variables. Transferring the animals from the nonaversive to the aversive environment (DeSilva et al, 1978b; Liang et al, 1979) resulted in a substantial 40 percent reduction in vulnerable period threshold (See Figure 2). These findings indicate that psychologic stress profoundly lowers the cardiac threshold for ventricular fibrillation.



(Figure 2) Effect of aversive sling environment on repetitive extrasystole (RE) threshold and circulating plasma catecholamine level. The RE threshold decreased 41 percent within 10 minutes of placing the animals in the sling after removal from the cage. The reduction in threshold was accompanied by substantial increases in both norepinephrine and epinephrine. Values are means +/- SEM. (From Liang et al, 1979, with permission.)

It was pertinent to determine whether the type of stress was crucial to the changes in ventricular vulnerability. We therefore examined an entirely different psychologic stress model in which dogs were subjected to programmed signaled shock avoidance (Matta et al, 1976b). Exposure to such an aversive conditioning program resulted in a 50 percent reduction in the repetitive extrasystole threshold, a change comparable to that observed in the cage-sling paradigm described above. Thus, the type of stress did not appear to be a critical factor to enhancement in ventricular vulnerability.

An important issue to be resolved was whether these moderate aversive psychologic states were sufficient in magnitude to provoke ventricular arrhythmias in the predisposed animal without the need to subject the heart to external electrical stimulation.

This question was examined in dogs subjected to coronary artery occlusion (Corbalan et al, 1974). The animals were conditioned according to the cage-sling paradigm. After five consecutive days in which they spend one hour in the cage and one hour in the sling, a balloon occluder previously implanted around the left anterior descending coronary artery was inflated. Once the animals had recovered fully from the occlusion and were entirely free of arrhythmia, they were reexposed to the two environments. The sling environment consistently resulted in diverse ventricular arrhythmias including ventricular tachycardia and R-on-T extrasystoles; these effects disappeared when the animals were returned to the nonaversive cage. In these dogs recovering from myocardial infarction, ventricular fibrillation was not precipitated, despite the consistent induction of serious arrhythmias. This was the case even when the animals were exposed to the aversive environment within only a few hours following occlusion of a major coronary vessel. It remained uncertain whether these psychologic stresses were of sufficient magnitude to trigger ventricular fibrillation.

To shed light on the question, we examined whether imposition of psychologic stress during the very inception of acute myocardial ischemia would predispose to ventricular fibrillation. Our experimental model involved a 10-minute period of left anterior descending coronary artery occlusion followed by abrupt release. This model was chosen becaue it exhibits a consistent time course of changes in ventricular vulnerability. Specifically, within one to two minutes of coronary occlusion, the vulnerable period threshold falls to extremely low levels. This period of enhanced vulnerability persists for six to seven minutes after which time the vulnerable period threshold recovers despite continued occlusion. Upon release of the occlusion after an ischemic period of 10 minutes, a brief period of vulnerability reappears within 20 to 30 seconds and lasts for less than one minute (Lown and Verrier, 1976).

An additional reason for choosing an occlusion-release model is that it is unclear whether the provocation of ventricular fibrillation in humans results from an ischemic lesion caused by infringement of arterial flow or from the release of obstruction with ensuing reperfusion such as might be observed with transient coronary artery spasm. The effects of the cage and the sling environments were therefore evaluated in the occlusion-release model. When acute myocardial ischemia was induced in the aversive sling setting, the incidence of ventricular fibrillation was more than three times greater (46 percent versus 14 percent, $p < 0.01$) than that observed in the nonaversive environment (Verrier and Lown, 1978a). The episode of ventricular fibrillation occurred within three to five minutes of coronary artery occlusion or within 20 to 30 seconds of release of obstruction. These intervals correspond closely with the periods of maximum ventricular vulnerability exposed by electrical testing of the heart.

Skinner and coworkers (1975a) have also reported a significant influence of psychologic stimuli on susceptibility to ventricular fibrillation during acute coronary artery occlusion in pigs. Myocardial ischemia was induced in either a familiar or unfamiliar environment. In the unfamiliar setting, following coronary artery occlusion, fibrillation occurred within a few minutes; however, onset of fibrillation was greatly delayed and even entirely prevented in some animals in an environment to which the pigs had been previously adapted.

These results indicate that diverse biobehavioral stresses are capable of lowering the vulnerable period threshold in the normal heart and predisposing the acutely ischemic heart to ventricular fibrillation during both occlusion and reperfusion. How then does higher nervous system activity conduce the ventricular myocardium to fibrillation?

Adrenergic Factors and Vulnerability During Psychologic Stress

Do adrenergic factors play a substantial role in mediating ventricular vulnerability during biobehavioral stress in conscious animals? This appears to be the case with respect to effects of aversive conditioning on ventricular electrical stability and is supported by several observations. First, the levels of circulating catecholamines vary directly with the changes in ventricular vulnerability during psychologic stress (Liang et al, 1979). When dogs were transferred from a nonaversive cage to an aversive sling environment, there was a substantial rise in blood epinephrine and norepinephrine concentrations indicative of enhanced sympathetic neural activity as well as adrenal medullary discharge. The

observed reductions in vulnerable period threshold corresponded with the concomitant elevations in circulating catecholamine levels (Liang et al, 1979).

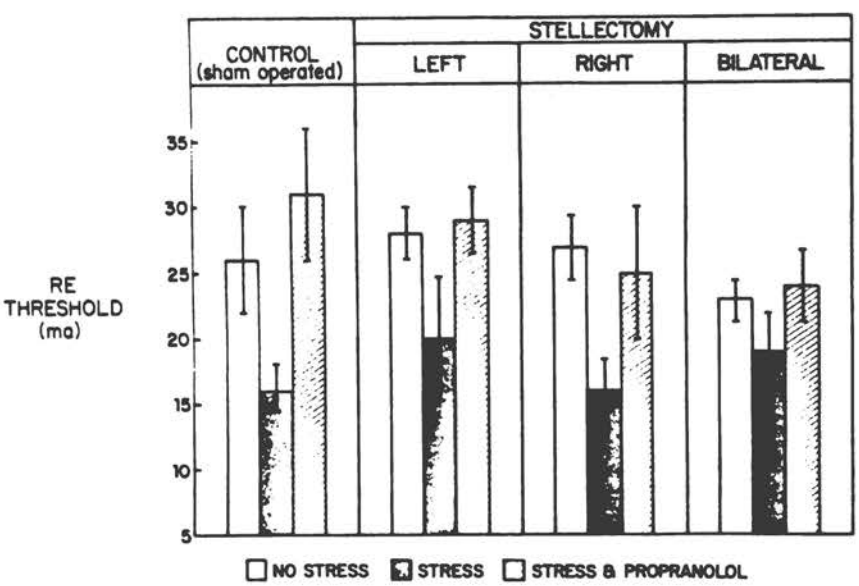
An essential involvement of adrenergic mechanisms is also suggested by the effects of pharmacologic and surgical sympathectomy on stress-induced changes in ventricular vulnerability (Matta, 1976a; Verrier and Lown, 1977). Indeed, they have shown that beta-adrenergic blockade with propranolol or the cardioselective agent tolamolol completely prevents the effects of aversive conditioning on the vulnerable period threshold (Verrier and Lown, 1977). This is the case whether the conditioning is classical or instrumental. It is of interest that stellectomy, whether of the left or right ganglion, did not prevent the reduction in repetitive extrasystole threshold associated with aversive conditioning. Verrier and Lown (1978b) demonstrated that only partial protection was conferred by bilateral stellectomy (Figure 3). Thus, adrenergic inputs, in addition to those derived from stellate ganglia, impinge upon the myocardium during psychologic stress to alter ventricular vulnerability. Most probably these additional inputs derive from other thoracic ganglia and from adrenal medullary catecholamines. In this respect, it is pertinent to note that in stellectomized dogs, plasma catecholamine levels, particularly of epinephrine, are markedly elevated in response to stress when compared to those observed in neurally intact animals.

Psychophysiologic Mechanisms During Myocardial Ischemia

The precise neural mechanisms involved in the biobehavioral provocation of ventricular arrhythmias during myocardial ischemia and infarction are only partially understood. For example, whereas farm pigs adapted to a laboratory environment have a reduced and delayed onset of ventricular fibrillation during coronary artery obstruction, surprisingly, beta-adrenergic blockage with propranolol did not afford any protection against the development of ventricular fibrillation in unadapted animals (Skinner et al, 1975a). Pharmacologic blockage of adrenergic input to the heart and environment adaptation did not yield equivalent results. It remains to be determined whether the failure of propranolol to protect against ventricular fibrillation resulted from inadequate blockade of adrenergic inputs to the heart or from the involvement of extra-adrenergic factors in the antifibrillatory effect of psychologic adaptation.

By contrast, Rosenfeld et al (1978) found a significant protective effect of beta-adrenergic blockage against malignant ventricular arrhythmias associated with acute coronary artery occlusion in dogs exposed to behavioral stresses. The animals were chronically instrumented to record electrocardiograms and

electrograms for ischemic and nonischemic ventricular epicardium during either left anterior descending or circumflex coronary artery occlusion. The dogs were exposed to several forms of behavioral stress experimentation in an unfamiliar environment, or were presented with stressful stimuli which were either a light followed by a sudden noise, or a noise followed by subcutaneous electrical shock. Shock significantly decreased latency and increased the grade of ventricular arrhythmias. Beta-adrenergic blockade with the cardioselective agent tolamolol substantially reduced the adverse effects of stress on cardiac rhythm. Moreover, they found that the quaternary analog of propranolol, UM 272, which causes no beta-adrenergic blockade but exerts direct local anesthetic effects on the heart, did not confer a protective action. Thus, the beneficial effect of tolamolol appears to result from its antiadrenergic action rather than from a nonspecific effect on myocardial tissue. These workers also demonstrated an antiarrhythmic effect of the antianxiety drug diazepam.



(Figure 3) Effect of beta-adrenergic blockade with propranolol (0.25 mg/kg) and stellectony on ventricular vulnerability during psychologic stress. Stree induced a significant decrease in vulnerable period threshold which decrease is prevented by propranolol. Unilateral stellectomy did not prevent the decrease in threshold and only partial protection was afforded by bilateral stellectomy. (From Verrier and Lown, 1978b, with permission.)

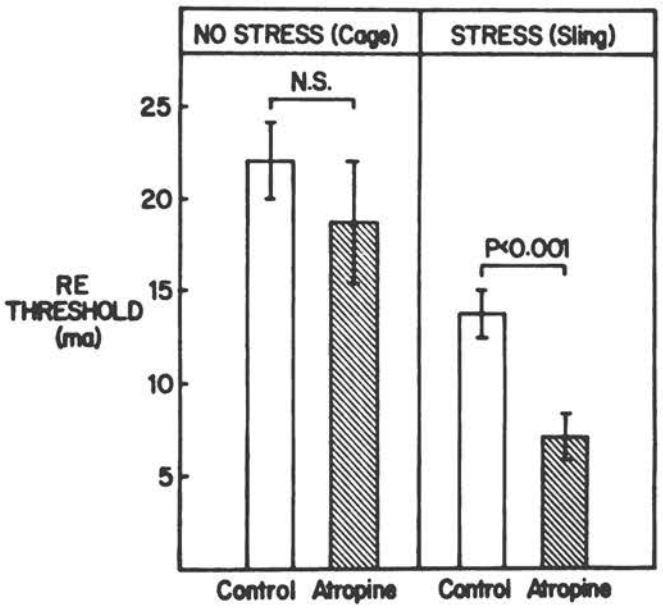
Cholinergic Influences and Vulnerability During Stress

Do cholinergic factors also modulate ventricular electrical properties in response to environmental stimuli? Two sets of observations suggest an affirmative answer to this question. First, it has been shown that administration of morphine sulfate to dogs in the aversive sling environment increased the vulnerable period threshold to the value observed in the nonaversive cage setting (DeSilva et al, 1978b). When vagal efferent activity was blocked by atropine, a major component of morphine's protective effect was annulled. When morphine was given in the nonaversive environment, where adrenergic activity was reduced as indicated by low circulating catecholamine levels, drug induced vagotonia did not affect the vulnerable period threshold (DeSilva et al, 1978b; Liang et al, 1979). Thus, the beneficial effect of morphine during psychologic stress appeared to result partly from vagal antagonism of the fibrillatory influence of enhanced adrenergic input to the heart and partly from the drug's sedative action.

It remained uncertain, however, whether intrinsic vagal tone in the stressed animal was sufficient to exert a stabilizing influence of ventricular vulnerability. To study this question, relatively small doses of atropine (0.05 mg/kg) were given to block selectively vagal efferent activity to the heart. In the aversive sling setting, vagal efferent blockade resulted in a substantial 50 percent reduction in the vulnerable period threshold. The implication is that in the stressed animal a considerable level of vagal tone is present which partly offsets the profibrillatory influence of aversive psychophysiologic stimuli. In the cage, where adrenergic input was low, Verrier and Lown (1980) demonstrated that vagal blockade was without effect on the threshold (Figure 4).

Sympathetic-parasympathetic Interactions

What then is the basis for the protective effect of the vagus on ventricular vulnerability? Our thesis has been that the effect of the vagus on ventricular vulnerability is contingent on the level of pre-existing cardiac sympathetic tone (Lown and Verrier, 1976a). At a low level of sympathetic tone, no vagus effect is demonstrated (Kolman et al, 1975). By contrast, when sympathetic tone to the heart is augmented by thoracotomy, sympathetic nerve stimulation, or catecholamine infusion, simultaneous vagal activation exerts a protective effect on ventricular vulnerability (Kolman et al, 1975; Rabinowitz et al, 1976). Vagus nerve stimulation is without effect on vulnerability when adrenergic input to the heart is ablated by beta-adrenergic blockade (Kolman et al, 1975; Rabinowitz et al, 1976).



(Figure 4) Influence of atropine (0.05 mg/kg) on repetitive extrasystole (RE) threshold in conscious dogs exposed to nonaversive and aversive environments. In the aversive setting, blockade of vagal efferent activity with atropine substantially reduced the vulnerable period threshold, indicating an enhanced propensity for ventricular fibrillation. In the nonstressful setting, where adrenergic activity was low, no effect of the drug was evident. Heart rate was maintained constant during cardiac electrical testing by ventricular pacing (Verrier and Lown, 1980).

The influence of the vagus on ventricular vulnerability appears to result from activation of muscarinic receptors, since these changes in vulnerability are prevented by atropine administration (Lown and Verrier, 1976). The diminution of adrenergic effects by muscarinic activation has a physiologic and cellular basis. Muscarinic agents inhibit the release of norepinephrine from sympathetic nerve endings (Levy and Blattberg, 1976) and attenuate the response to norepinephrine at receptor sites by cyclic nucleotide interactions (Watanabe and Besch, 1979).

Thus, results from both anesthetized and conscious animal experiments indicate that enhanced cardiac vagal tone, whether occurring spontaneously or induced pharmacologically, decreases susceptibility to ventricular fibrillation. This beneficial action is primarily caused by antagonism of adrenergic inputs to the heart.

Vagal Influences in the Ischemic and Infarcted Heart

It remains unknown whether enhanced vagal activity alters cardiac predisposition to VF during acute coronary artery occlusion. Kent et al (1973) found that vagus nerve stimulation significantly increased the VF threshold and decreased susceptibility to fibrillation in the ischemic canine heart. Subsequently, Corr et al (1974, 1976) observed that the presence of intact vagi protected against VF in chloralose-anesthetized cats during left anterior descending coronary artery ligation, but was not beneficial during right coronary artery obstruction. Yoon et al (1977) and James et al (1977) were unable to demonstrate any effect of vagus nerve stimulation on VF threshold during left anterior descending coronary artery occlusion in the canine heart. Corr and coworkers (1978) have even found that cholinergic stimulation may exacerbate rather than ameliorate the arrhythmias which ensue upon release of occlusion, with attendant reperfusion of the ischemic myocardium.

We have found that intense cholinergic stimulation by electrical stimulation of the decentralized vagi or by direct muscarinic enhancement with methacholine affords only partial protection during myocardial ischemia in dogs in which heart rate was maintained constant by pacing. (Verrier and Lown, 1978b) No salutary influence of cholinergic stimulation, however, was noted during reperfusion. However, additional countervailing factors come into play when myocardial perfusion is impaired. Thus, vagal stimulation does not completely suppress the arrhythmias which result from myocardial infarction (Kerzner et al, 1973). In fact, it has been found that enhanced vagal activity or acetylcholine infusion consistently elicited ventricular tachycardia during the quiescent arrhythmia-free phase of myocardial infarction in dogs. This effect was completely rate dependent since preventing the vagally induced bradycardia abolished the arrhythmias. Thus, the antiarrhythmic effects of the vagus may be augmented or reversed by its profound influence on heart rate in the setting of acute myocardial infarction.

Final Comments

The above-cited studies emphasize the importance of neural and psychologic factors in the genesis of ventricular arrhythmias. In particular, the sympathetic nervous system appears to be a primary mediator of ventricular vulnerability, whereas the efferent vagus nerve appears to antagonize the arrhythmogenic influence of adrenergic inputs to the heart. This suggests that an important strategy for clinical management of malignant ventricular arrhythmias will require lessening cardiac sympathetic drive while enhancing vagal tone. To this end, we have begun to examine whether neurochemical agents which induce such a pattern of autonomic neural outflow may thereby protect against ventricular arrhythmias. The results (Table 3) to date have been most encouraging and support the concept that containment of neurophysiologic triggers may indeed provide a powerful therapeutic tool.

TABLE 3 - CENTRAL NEUROCHEMICAL AGENTS WHICH DECREASE VENTRICULAR VULNERABILITY

Agent	Proposed mechanism	Comment
Clonidine (Rotenberg, et al, 1978)	Decreases cardiac sympathetic tone by enhanced afferent vagal input to midbrain cardiovascular regulatory centers	Does not protect against VF during myocardial ischemia or reperfusion.
Morphine sulfate (DeSilva et al, 1978)	Increases vagal efferent tone and decreases sympathetic tone due to sedative action	Decreases vulnerability during psychological stress
L-Tryptophan + (Phenylzine and carbidopa) (Rabinowitz, and Lown, 1978)	Decreases sympathetic tone by increasing brain serotonin level	Effect during myocardial ischemia unknown
Tyrosine (Scott, et al, 1981a, 1981b)	Decreases cardiac sympathetic tone through central catecholeminergic mechanisms	Effect during myocardial ischemia under investigation

THE ROLE OF CORONARY ARTERY SPASM IN LIFE-THREATENING ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

Eugene Braunwald, M.D.
James Muller, M.D.

We would like to present information which indicates that coronary spasm can occur and that the acute myocardial ischemia that coronary spasm produces might be responsible for some serious arrhythmias. We will also review some pharmacologic means which can be used to interrupt this process.

The hypothesis that constriction of the coronary arteries could play a role in ischemic heart disease has been present in the literature since the earliest descriptions of angina pectoris. In particular, at the turn of the century, William Osler, in his lectures on angina pectoris, attributed the episodic chest pains to coronary spasm (Osler, 1910).

There was a long hiatus between Osler's hypothesis and proof of the existence of coronary spasm. For about 60 years, the notion that coronary vasoconstriction was important, or that it actually could occur, was not considered to be likely. We think this resulted from the observation at postmortem examinations that markedly obstructed coronary vessels were generally present. It was thought that these obstructed vessels could not conceivably constrict.

The necessary change in thinking occurred in 1959 when Prinzmetal and his colleagues described a special subgroup of patients with "variant angina", characterized by pain at rest accompanied by reversible ST segment elevation in the electrocardiogram (Prinzmetal et al, 1959). The episodic rest pain in these patients was attributed to coronary spasm. Thereafter, coronary spasm was demonstrated angiographically in a number of laboratories (Oliva et al, 1973; Miller, 1976).

As these clinical observations were being made, evidence was developed in research with experimental animals which indicated an important role for primary changes in the diameters of coronary arteries. Until the mid-1960s, there was very little physiologic evidence for any important regulation of the coronary vascular bed by anything other than the products of metabolism. This primarily

resulted from the fact that most studies were conducted in anesthetized animals. When conscious, instrumented animals were studied, the results were quite different. Norepinephrine produced different effects on the coronary circulation when injected into conscious versus anesthesized dogs. In the anesthetized dog, norepinephrine produced coronary vasodilation -- that is, the neural factors were not evident -- and in the conscious dog, norepinephrine injection led to coronary vasoconstriction.

Thus from the experimental work, it is now quite clear that coronary vascular resistance and coronary diameter can change as a consequence of a variety of neural and pharmacologic stimuli. What is the evidence that such events occur in man? There is now a variety of findings indicating that clinically significant coronary vasoconstriction occurs.

As mentioned previously, Prinzmetal's angina is the condition that provided the primary evidence that spasm is important in clinical cardiology. It has now become clear that there are many other ischemic cardiac conditions, in which coronary spasm may play a role. Masseri has presented very convincing evidence that in patients with angina at rest, without ST segment elevations -- that is, without the classic picture of Prinzmetal's angina -- there may be profound coronary vasoconstriction (Maseri, 1979). He obtained continuous recordings of coronary sinus oxygen saturation in a patient who was being monitored in a coronary care unit. The patient had four separate episodes of pain at rest. The very first event that occurred was a reduction in the coronary venous oxygen saturation. This preceded the development of pain and the appearance of electrocardiographic changes. So the pain that occurs under these circumstances appears to follow the development of ischemia. The tachycardia, the increase in arterial pressure, and the increase in oxygen needs follow the development of ischemia rather than precede it. It is, therefore, likely that a reduction of coronary flow, probably brought about by coronary spasm, is the cause of ischemia.

In our laboratory, with Drs. Mudge and Grossman, we have observed that the vast majority of patients with stable angina can be demonstrated to have inappropriate coronary vasoconstriction under certain circumstances (Mudge et al, 1976a, 1976b). We have measured coronary blood flow by two techniques. The thermodilution method has been used to continuously record coronary sinus outflow. We employed the cold pressor test -- that is, placing a hand into ice water and leaving it immersed for 50 seconds -- as a stimulus to coronary constriction. In normal individuals there is an increase in arterial pressure, and an increase in coronary sinus flow. The calculated coronary vascular resistance shows no significant change. In patients with arteriographically proven coronary artery

disease, however, the situation is quite different. There is an increase in arterial pressure, as in normals, but there is a marked reduction in coronary sinus flow. Those patients who developed angina had a much greater increase in coronary vascular resistance than those who did not develop angina during the cold pressor challenge. This increase in coronary vascular resistance during the cold pressor test could be abolished by pretreatment with either phentolamine or phenoxybenzamine alpha-adrenergic blocking agents.

So, there is evidence that under certain circumstances, one can elicit coronary vasoconstriction in almost all patients with stable coronary artery disease.

Coronary vasoconstriction also appears to occur during exercise in a subset of patients. In Japan, Yasue and collaborators (1979) exercised a group of patients with Prinzmetal's angina, and some of them developed pain and ST segment elevations during exercise. One of these patients was treated with a calcium channel blocking agent, diltiazem, which prevented the pain and ST segment changes. When the patient was treated with propranolol, a nonspecific beta blocking agent, which blocks both $beta_1$ and $beta_2$ adrenergic receptors, there was actually an increase in the ST segment elevation. This was probably due to the $beta_2$ blocking effects of the drug, which inhibit coronary vasodilator influences which are transmitted through the $beta_2$ receptors.

Finally, we would like to discuss the precipitation of coronary spasm by emotions. Drs. Frederic Schiffer and Walter Abelman and their colleagues have introduced the quiz electrocardiogram, an uncomfortable way of challenging people intellectually (Schiffer et al, 1976). Executives, who often have a type A behavior pattern, are particularly vulnerable to the stress of the quiz electrocardiogram. In an early study, 10 of 14 executives with a history of angina pectoris developed more than 0.5 mm ST segment depression during emotional stress. These changes occurred in conjunction with increases in heart rate and systemic arterial pressure. The electrocardiographic changes were virtually identical to those observed during exercise.

This might be considered an interesting observation with little or no relationship to coronary spasm. Emotional stress can easily produce elevations in heart rate and blood pressure which then increase myocardial oxygen demands, as does physical exertion. As a matter of fact, the group's mean systemic arterial pressure increased from 136/87 mmHg to 158/94 mmHg during the quiz. Heart rate also increased from 76 to 87 beats per minute. It could have been that the ischemic changes observed in these patients were due solely to increases in oxygen demand.

Dr. Schiffer and his colleagues then extended these observations (Schiffer et al, 1980). They utilized as an index the product of the heart rate and systolic pressure, the so-called double product. It is a reasonably good measure of myocardial oxygen demand. The study was conducted in 36 patients with angina pectoris. Twelve of these developed greater than 1 mm ST segment depression during the emotional stress of the quiz. Routine exercise tolerance tests were then performed in these twelve. The double product at the time of peak ST segment depression during the quiz was then compared to the double product at the time of appearance of an equivalent amount of exercise-induced ST segment depression. During emotional stress the double product was only 181 $\pm$ 64 (S.D.) $x10^2$ while during exercise it was 225 $\pm$ 54 (S.D.) $x10^2$ implying that myocardial ischemia occurred at a time of lower oxygen demand during emotional stress than during exercise. The double product does not reflect changes in myocardial contractility which might have occurred. However, during exercise the heart rate was higher than during emotional stress, indicating that adrenergic activity (and its attendant increase in contractility) was greater during exercise.

These findings indicate that something other than an increase in myocardial oxygen demand produced ischemia during emotional stress. Otherwise, the product of heart rate and blood pressure at which ischemia occurred would have been identical under the two circumstances, here the observed difference was quite sizeable. It is likely that the ischemia observed during emotional stress resulted from a decrease in oxygen supply caused by coronary vasoconstriction.

In some cases the ischemia produced by coronary spasm can have very serious consequences. In a study of 127 patients with Prinzmetal's angina, 34 percent had experienced ventricular tachycardia and 13 percent had had an episode of ventricular fibrillation (Antman et al, 1980). Sudden cardiac death could result from such a process.

There are some new pharmacologic agents which are of value in the treatment of coronary spasm -- they belong to a group termed the "calcium channel blocking agents". We described previously our observation, in the laboratory, that the cold pressor stimulus produces an inappropriate increase in coronary vascular resistance in patients with arteriographically proven coronary artery disease. We performed cold pressor tests before and another after administration of the calcium channel blocker nifedipine. Prior to nifedipine the cold pressor stimulus produced an increase of about 20 percent in coronary vascular resistance. Following nifedipine the same patients failed to show an increase in coronary vascular resistance during the cold stimulus -- they actually showed a modest degree of coronary vasodilatation (Gunther et al, 1981).

How useful is nifedipine? Together with investigators in a number of laboratories, we have accumulated information on 127 patients with Prinzmetal's angina who were treated with nifedipine (Antman et al, 1980). It is known that this rare disease is caused by spasm. The patients were identified on the basis of episodic chest pain accompanied by reversible ST segment elevation. In some, coronary spasm was demonstrated at cardiac catheterization. The results of treatment with nifedipine are shown in Figure 1. The number of attacks of chest pain fell strikingly from a mean of 16 in the week before initiation of nifedipine to a mean of two in the last week of observation on nifedipine therapy. Sixty-three percent of the patients had complete elimination of their attacks.

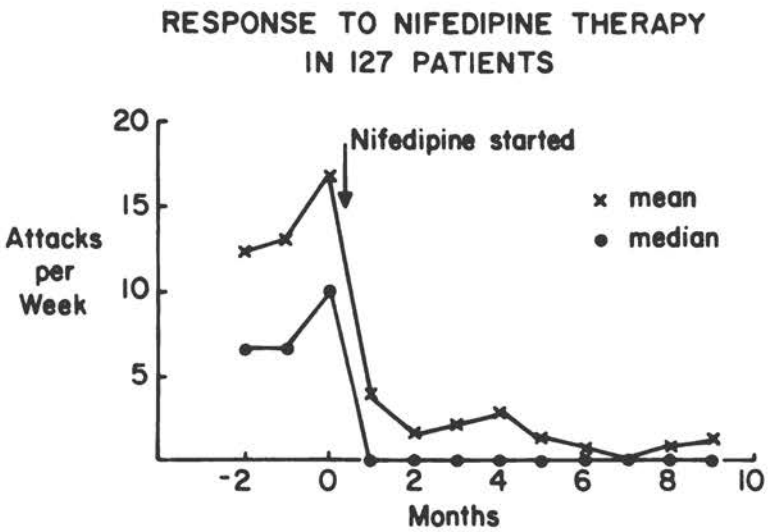


Figure 1.

The role of variable obstruction in causing the attacks of Prinzmetal's angina is quite well accepted. In patients who do not have Prinzmetal's angina, variable obstruction may also play a role. Some patients may develop myocardial ischemia from a combination of a fixed obstruction and a variable obstruction. The variable obstruction may be due to spasm or coronary artery vasoconstriction.

Treatment of the variable obstruction is possible by means of nifedipine, nitroglycerin, and other agents which relieve spasm. In

patients who have marked fixed obstruction with little variable obstruction, these coronary vasodilators cannot be expected to have much effect. Such patients can be treated with beta-adrenergic blockers to diminish oxygen demand or coronary artery bypass grafting to improve oxygen supply. On the other hand, in patients who have very little fixed obstruction, coronary vasodilators may be quite effective.

In summary, there is extensive evidence that coronary artery spasm may be an important contributor to many forms of ischemic heart disease including sudden cardiac death. In patients known to have spasm, it can be prevented and can be blocked by treatment with a calcium channel blocking agent. The role of this mechanism and its potential treatment are important areas of future research on the enormous problem of sudden cardiac death.

TOWARD A CARDIOVASCULAR NEUROBIOLOGY

David H. Cohen, Ph.D.

I would like to deal with two issues: first, to define "cardiovascular neurobiology", and second, to comment upon how this emerging field might relate to sudden cardiac death.

For at least a century, we have had convincing experimental evidence that the nervous system is involved in the regulation of the heart, and substantial anecdotal information long precedes this. Where have these early observations led us? (1) We have seen a proliferation of epidemiological studies implicating environmental, social, and psychological factors in the etiology of cardiovascular disease. (2) We have witnessed the development of controlled behavioral models for investigating stimulus-induced cardiovascular changes, normal and abnormal, including demonstrations of the potential importance of learning. (3) We have seen the development of physiological models in which brain stimulation, brain lesions, or pharmacological intervention can reliably produce cardiovascular pathology. (4) Finally, we are in the midst of an explosive growth of cardiovascular neuropharmacology, most prominently involving the biogenic amines and pointing toward the involvement of neuropeptides as well.

Our present challenge is to begin weaving these exciting strands into a more systematic assault on the relationship between the brain and cardiovascular system. I would suggest that such a "cardiovascular neurobiology" must be firmly anchored in a rigorous understanding of the neural pathways that influence cardiovascular function, an issue alluded to by Dr. Verrier in his plenary presentation at this conference. This is, perhaps, the least common denominator in developing an effective "cardiovascular neurobiology".

Contemporary advances in understanding the brain have most frequently been rooted in a rigorous connectionistic approach with the neuron as the basic unit of analysis. Until quite recently, such approaches have not been applied with sufficient intensity and perseverance to the neural control of cardiovascular function. In my view, this has been the rate-limiting step in the development of the field, and I would like to offer some suggestions as to why this may have occurred.

Historically, neurophysiologists have tended to avoid the autonomic nervous system in part because of early theoretical formulations characterizing it as diffusely organized. This, and the long latencies of effector action, were incompatible with the conceptual and technical center of gravity of cellular neurophysiological analysis which has a time domain of milliseconds. Compounding this was the difficulty in identifying central autonomic pathways with the available neuroanatomical methods. We now know that this reflected an insufficient sensitivity of the silver techniques for staining certain types of pathways.

Regarding the cardiovascular physiologists, my impression is that they tended to minimize the extent to which the brain might be involved in cardiovascular disease. Most were not appropriately trained to pursue such issues, and their efforts were focused more on peripheral reflex mechanisms. This generated, for example, a voluminous literature on baroreceptors that did not even include information regarding the central terminations of baroreceptor afferents.

Many of the technical and conceptual difficulties have now been surmounted, and an appropriate Zeitgeist exists for rapid advances. However, the substantial contributions being realized seem limited to but a few laboratories. Perhaps this reflects a general decline in interest among neuroscientists in more integrative neurobiological problems, in turn reflecting the current excitement with advances in cellular and molecular neurobiology. Nevertheless, the foundation exists to meet the challenge of unravelling the relevant central circuitry and for undertaking the rigorous investigation of neural involvement in cardiovascular disease. The experimental tools are available and only need be applied to provide the anatomical and physiological basis for the development of effective experimental models. Were this potential to become sufficiently visible and attractive to neurobiologists, perhaps we could recruit the critical mass of appropriately trained investigators to capitalize upon it.

I would now like to turn to the possible role of a "cardiovascular neurobiology" in the context of sudden cardiac death. If one accepts the premise, clearly evident at this meeting, that the central nervous system indeed plays a significant and perhaps even dominant role in initiating the arrhythmias leading to sudden cardiac death, then I would view the following tasks as confronting us: (1) The neural pathways involved must be delineated. (2) The discharge patterns along these pathways that are associated with the initiation of arrhythmia must be determined. (3) How such discharge patterns are generated by internal and external stimuli must be described. (4) We should explore the extent to which neuronal modifiability can produce

persistently abnormal cardiac rhythms. (5) We must explore means of manipulating activity along these relevant pathways to prevent or reverse pathological effects.

Where might one begin in this effort? Significant contemporary advances in other neural systems, such as sensory systems, have been facilitated considerably by the capability of studying how they transform information over successively central relays, beginning at the receptors. Such a systematic analysis from the periphery centrally can also be applied to motor systems, and for neural control of the heart this implies initiating analysis at the cardiac innervation and proceeding centrally from this final common path.

With respect to cardiac arrhythmia, an important beginning is at hand based upon the findings of such investigators as Lown, Schwartz, and Stone that in the ischemic heart a unilateral increase in sympathetic outflow or an imbalance between left and right sympathetic cardiac influences can predispose the heart to ventricular fibrillation. These patterns of activity are in all likelihood generated by suprasegmental influences upon the sympathetic preganglionic neurons that project upon the cardiac postganglionic cells. Thus, we must first establish the basic organization of these preganglionic cells, their projection patterns upon identified postganglionic neurons, and the descending systems that influence preganglionic activity. Given such information, one could then begin exploring the specific descending pathways capable of initiating arrhythmia and the conditions under which this can occur.

It is only very recently that we have begun to appreciate the central pathways but one step removed from the final common path. A suggested summary of our present knowledge in this regard is presented in Figure 1. Moreover, with the exciting advances in neuropharmacology and immunohistochemistry, we are beginning to gain information regarding possible transmitters of these descending pathways. This is but the first step in pursuing a systematic analysis from the periphery centrally. Yet, even at this preliminary stage there are some tantalizing possibilities supporting the contention that the time is appropriate for a productive convergence of various lines of research into a true "cardiovascular neurobiology" that could bear upon the pathophysiology of sudden cardiac death.

I would like to complete my presentation by providing one illustration of such convergence. As described by Dr. Verrier, Lown's group has shown that with the ischemic heart various alterations in sympathetic outflow can produce ventricular fibrillation. Moreover, they have shown that various means of reducing the sympathetic outflow can raise the threshold for

ventricular vulnerability. In this regard, Rabinowitz and Lown (1978) have recently reported that increasing brain serotonin levels by administering serotonin precursors reduces the sympathetic outflow and increases the threshold for ventricular vulnerability by 50 percent in experimental dogs. These investigators did not explore possible mechanisms of this protective effect.

From a line of research motivated by quite different considerations, Cabot and I found that the most prominent area of serotonergic neurons in the brain, the raphe nuclei, includes cell groups that project directly upon the sympathetic preganglionic neurons. Stimulating this brainstem region produces a fall in both systolic and diastolic pressure, as well as heart rate changes. Moreover, by recording the activity of individual preganglionic neurons we could show that raphe stimulation decreased their discharge, and Cabot and Guyenet have recently found that a similar effect is obtained if serotonin is iontophoresed upon preganglionic neurons. Finally, we were able to show that if this raphe-spinal system is interrupted by lesions, then heart rate responses to various stimuli become highly labile, being of considerably greater magnitude than normally elicited by those stimuli.

These findings may contribute to understanding the results of Lown and Rabinowitz (1977b). Our results suggest that this raphe-spinal system may serve an important rate-limiting function by inhibiting sympathetic preganglionic activity and thus sympathetic outflow. Since the involved transmitter is likely to be serotonin, then raising serotonin levels might simulate activation of this pathway. By no means can it be definitely concluded at present that this raphe-spinal pathway mediates the Lown and Rabinowitz effect, much less that it is involved in the malignant arrhythmias precipitating sudden cardiac death. The important point, however, is that as we learn more regarding the organization of the central pathways influencing cardiac dynamics, the more instances we can anticipate of productive convergence of the diverse research directions in the field.

In conclusion, I am suggesting that an enhanced effort to unravel the central circuitry involved in the neural control of cardiovascular activity is well within our technical capability and that this would constitute the least common denominator of a contemporary "cardiovascular neurobiology". Understanding such pathways would provide the necessary foundation for developing physiological model systems for exploring the role of the brain in cardiovascular disease, and this in turn is the requisite foundation for ultimately understanding how environmental and psychological factors contribute to cardiovascular pathology. I genuinely feel that we are on the threshold of exciting advances and that the field can indeed be made attractive to appropriately trained scientists who are important to our realization of such advances.

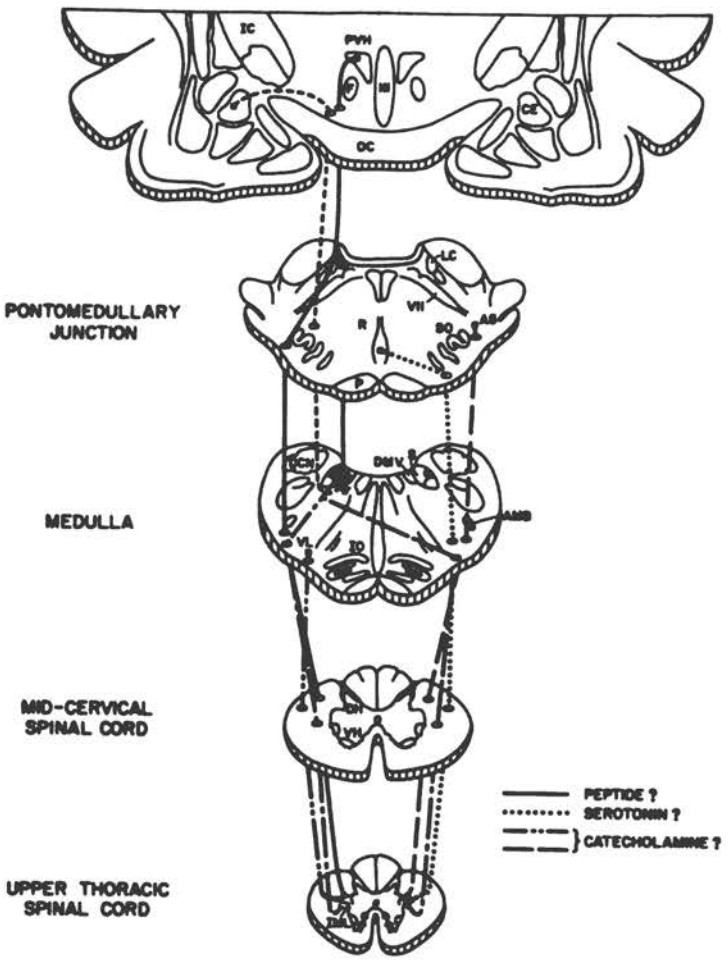


Figure 1. Schematic summary of recently identified descending pathways that project directly upon the dorsal motor nucleus of the vagus and/or the sympathetic preganglionic cell column. The hypothesized transmitters of four of the six pathways are indicated. A5: A5 catacholamine cell group of Dahlstrom and Fuxe; AMB: nucleus ambiguus; CE: central nucleus of the amygdala; DCN: dorsal column nuclei; DH: doral horn; DMV: dorsal motor nucleus of the vagus; F: fornix; IC: internal capsule; III: third ventricle; IML: intermediolateral cell column; IO: inferior olive; LC: locus coeruleus; OC: optic chiasm; P: pyramid; PVH: paraventricular nucleus of the hypothalamus; R: raphe nucleus; S: solitary nucleus; SO: superior olive; VH: ventral horn; VII: facial nerve rootlets; VL: ventrolateral medullary region including the adrenaline and nonadrenaline-containing cell groups.

(This presentation was based in large part upon an article by Cohen and Cabot entitled "Toward a Cardiovascular Neurobiology," which appeared in the journal Trends in Neuroscience of November 1979.)

SUMMARY OF WORKSHOP A

PREVENTION OF SUDDEN CARDIAC DEATH: IDENTIFYING UNDERSTANDING AND MODIFYING BEHAVIORAL RISK FACTORS*

CHAIR: C. David Jenkins
VICE-CHAIR: Oglesby Paul

Participants: W. Castelli, F. Cohen, W. Greene, T. Hackett, L. Hinkle, R. Murray, H. Pincus, W. Ruberman, S. Weiss, M. Weissman

IOM Staff: F. Solomon, C. Carney

Basic strategic questions for the workshop included the predictive value of behavioral and biological risk factors, whether the contribuion of behavioral factors is large enough to make their reduction cost-effective in a public health context, the independence of biological and other known risk factors from behavioral risk factors or indicators, and the possibility of more effective alteration of behavior.

Some risk factors that need attention already are widely recognized, such as smoking cigarettes and not taking medication for hypertension, but it still is difficult for health workers to enlist the cooperation of persons at high risk. Workshop A participants agreed that research is needed to improve ways to change behavior known to constitute risk factors for coronary disease and sudden cardiac death.

In dealing with the general problem of our workshop we quickly found that we were talking at several levels with regard to the stage of the disease. Some risk factors are quite obviously related to the underlying conditions that lead to sudden cardiac death, or that raise the long-term risk of it. Other risk factors, both biological and behavioral, seem related to the final acute illness which may begin anywhere from weeks to hours to minutes before death. Still other pathological mechanisms take over only in the terminal episode which by definition is only a few minutes in duration.

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*Summary prepared by Dr. Jenkins

In addressing the issue of the validity of risk indicators, we decided we would have to pay attention to the stage of disease at which the risk indicator might be operative. We distinguished two levels: first, the underlying condition or the building up of disease substrate for sudden death, and the second, precipitating factors in final hours or days immediately preceding death. Our risk indicators were dealt with separately for those two stages of the disease.

The group next developed a lengthy list of possible social and behavioral risk indicators without, for the moment, considering the strength of the evidence to support them. Perhaps 20 or so variables were mentioned in this connection.

We then decided we needed to categorize these putative risk indicators according to an estimate based on current knowledge of the likelihood of the indicator being a valid predictor. We defined five levels as follows:

1. Probable predictors for which we could cite one or more good research studies with findings directly implicating or demonstrating the risk potential of the given behavior factor.

2. Possible predictors for which there was indirect evidence or evidence from less sound studies.

3. Plausible predictors for which there was only clinical lore or series of case reports as supporting evidence.

4. No current evidence on predictor.

5. Negative findings: i.e., when there was evidence the factor was not a predictor of sudden cardiac death.

After much discussion and difference of opinion, and, finally, very surprising consensus, we were able to rank some of these behavioral risk factors in terms of their likelihood of being a predictor.

"Predictor" in the context of our workshop, did not mean a contributing cause. We were only asking whether there was evidence that a statistical correlation better than chance could be made of the stated characteristic and risk of sudden cardiac death. It is possible that a variable can be a predictor and have no etiological involvement in the processes leading to sudden cardiac death. Both a predictor and SCD may be secondary to another factor; for example, depression and fatigue could be secondary to low socioeconomic status or to a chain of severe life changes.

A second point is that, even if a variable was not secondarily associated but had a primary association with the outcome variable, it might not be a very strong predictor when other risk factors were taken into account. This, of course, could only be determined in controlled studies with appropriate statistical design and analysis to determine the independent contributions of individual variables within a group of such variables to prediction of an outcome. In general, these studies have not been done.

We did not concern ourselves with whether a behavioral risk factor was modifiable. Some risk factors, although not modifiable, are useful in that they can help identify high risk populations for which other risk factor interventions should be given particularly higher priority. An example of this is family history of coronary disease or early sudden death. One cannot modify the family history, but it certainly helps in clinical management to know that this is an identifier of a higher risk person.

We were hoping, before the end of our allotted meeting time, to be able to talk further about what additional interventions should be initiated in efforts to prevent sudden cardiac death, and how likely this was to pay off in reduced risk of sudden cardiac death. But we weren't able to proceed that far. We did, however, get to the point of identifying a number of behavioral risk factors that we considered to be at Level 1, a probable predictor, or at Level 2, a possible predictor. These are listed in Table 1. Detailed documentation of the extensive literature mentioned or alluded to by workshop members during the discussion periods is beyond the scope of this summary.

As mentioned earlier, we distinguished between acute precipitating factors for sudden cardiac death and the underlying conditions that raised sudden cardiac death risk, such as by contributing to myocardial pathology, atherosclerosis, fibrosis, or other deleterious modifications of heart structure. The latter are contributors to the long-persisting development of risk and vulnerability.

Although there was no unanimity among the research findings, one or more studies suggested that each of the following variables may be "probable predictors" of sudden cardiac death: chronic life stressors, depression, anxiety, intense dissatisfaction with job and retirement, Type A behavior, lack of social support, low educational level, cigarette smoking, disturbed sleep patterns, lack of regular exercise, irregular episodes of unusually strenuous exercise, and excess alcohol use. These are shown in Table 1.

The workshop next identified as possible predictors those variables for which we have less direct evidence but still find some likelihood of contributing underlying conditions for sudden cardiac

TABLE 1

Social and Behavioral Factors That Appear To Be Associated With Underlying Conditions That Raise Risk For Sudden Cardiac Death

Probable Predictor (one or more direct findings)

Chronic life stressors
Depression/anxiety
Attitudes toward job and retirement
Type A behavior pattern
Absence of social supports
Low educational level
Cigarette smoking
Disturbed sleep patterns
Absence of regular exercise (aerobic)
Excess alcohol use
Lifelong cultural patterns of diet and related lifestyle

Possible Predictors (less direct evidence)

Acute life stressors
Paterns of dietary intake
"Personality" (measured by Minnesota Multiphasic Personality Inventory or 16 Personality Factor Scales)

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death. We included the following as possible predictors: acute life stressors; eating habits; and certain personality variables as yet not that well defined, but for example certain elements on the MMPI such as hysteria and hyperchondriasis which were found associated with higher risk for future angina pectoris. They may also raise the risk, in turn, for myocardial ischemia and sudden death. Similar findings have been on occasion reported for certain of the scales of the 16 Personality Factor Inventory.

There was a debate about eating habits: some workshop members felt that that was one of the strongest predictors, but others felt it had a weak association, particularly when directly measured in human populations. The workshop's consensus was that it should be rated as either a probable or a possible contributor to the long-term development of the foundations for sudden coronary death.

Exercise was seen as a possible risk factor in the negative sense and also in the positive sense. The gist of the evidence as we reviewed it was that regular aerobic exercise was protective in

that it reduced the risk of severe atherosclerosis and myocardial infarction, but acute strenuous exercise, particularly where that is not a regular pattern in the lifestyle of the individual, was often accompanied by severe tachycardia and sometimes ventricular fibrillation. There have been numerous clinical reports of such deaths.

When we looked at the acute phase of sudden cardiac death -- and by this we referred to roughly the last few days or weeks -- we found a fewer number of psychological and behavioral variables which have been implicated. The published studies vary in their definition of the prodromal period, and also in the definition of sudden cardiac death. The risk indicators found in our review are listed in the next table. Depression, anxiety, low educational level, fatigue and exhaustion, are all quite frequently reported. A review of that material was presented yesterday afternoon in conference plenary presentations.

TABLE 2

Social and Behavioral Factors That Appear To Be Associated With The Acute Phase of Sudden Cardiac Death

Probable Predictors (one or more direct findings)

- Depression/anxiety
- Low educational level
- Fatigue/exhaustion

Possible Predictor (less direct evidence)

- Acute life stressors
- Attitudes toward job and retirement
- "Type A"
- Unaccustomed strenuous exercise -- precipitates

Note: The social and behavioral factors listed here are not necessarily acute or episodic in their nature. They are listed if one or more controlled research studies has shown them predictive of acute life-threatening arrhythmias or sudden cardiac death.

Now, the important question: Are we ready for intervention on any of these factors? The workshop did not have the opportunity of discussing this issue directly due to lack of time. Dr. Paul and I therefore took the liberty of meeting as a subcommittee of two and submit the following opinions for your consideration. It was our belief that there were four behavioral factors which were ready for

community intervention programs of a behavioral change nature. Those deal with (1) cessation of cigarette smoking; (2) exercise, in two ways: fostering the habits of regular aerobic exercise and cautioning against sudden bursts of acute strenuous exercise, particularly in people of older ages where subclinical myocardial damage might be present; (3) changes in eating habits, both to lower serum lipids and to reduce obesity; and (4) warning against excess alcohol intake which has a demonstrated relationship to cardiomyopathy and also some evidence for exacerbating the irritability of the myocardium.

We found some other variables, not ready for community programs, but ready for controlled investigations, either animal or human or both, or possibly ready for selective use by physicians who find it indicated in individual cases. Among these variables are depression, fatigue, and exhaustion, Type A behavior, and perhaps some supportive interventions in the face of severe life crises (such as death of a spouse or other chains of traumatic events).

We did not get into the issue of how modifiable these factors are or how beneficial it would be to modify some of the other behavioral risk factors which are listed.

But I will let Dr. Paul, who served ably to keep us on keel and on course during our workshop meetings yesterday afternoon and this morning, add his comments at this point.

COMMENTS ON WORKSHOP SUMMARY

DR. OGLESBY PAUL (Workshop Vice-chair): I think Dr. Jenkins has very well summarized what the workshop group discussed. I might just make one brief comment here. I remember ten years ago when we made our report for the Task Force on Arteriosclerosis, a task force which included considering sudden death, that we did conclude that certain risk factors were ready for community preventive efforts. But we felt at that time there was very little satisfactory scientific evidence suggesting or recommending intervention in relation to personality disorder or other behavioral attributes, other than the ones that Dr. Jenkins mentioned today. I think at that time we did not include alcohol in terms of a relation to sudden death, perhaps partly because the information was not as adequate as it is at this time.

Now in 1980, ten years later, looking at this, it is obvious that we have amassed a great deal more useful and intriguing information than we had at that time, and that is, of course, very encouraging. I think, however, when one looks at the particular subject that our working group had, which was prevention, we are

very much in the same position as we were in 1970 in terms of intervening, if it is justified in terms of depression, fatigue, Type A personality, and some of the others which he listed on the board. I think we recall the wisdom of considering the behavioral aspects of smoking, of nutrition and obesity, and so forth. And in a sense, it has undoubtedly served a very useful purpose.

I would hope that in another ten years, when a similar meeting is called, that we may have some information as to how much one can modify some of these behavioral factors, and if one can modify them, what does it do to risk.

DR. PAUL (later comment): We tried, in speaking for those of us who are in Workshop A, we tried to identify studies which would justify the recommendations we made regarding specific areas. In relation to exercise, we had two points of view. I think Dr. Eliot is particularly referring to the one that suggests that regular exercise may be preventive, rather than the one that extreme exercise may be hazardous.

In relation to that one recommendation, we were referring to studies which include those of Ralph Paffenbarger. Paffenbarger, you may know, has done considerable work with several population groups. One is the longshoremen on the West Coast, where he has been interested in observing the effects of exercise in this group. A second group is the Harvard alumni group in which information obtain over many years through questionnaires, suggests that indeed those alumni who have had a regular vigorous exercise routine, seem to have lower heart attack rates than those who were more sedentary.

Similar information has been obtained from other studies. Many years ago, Dr. Morris in England published information on that. I think that perhaps Dr. Castelli might like to speak about the views of the Framingham group that slothfulness, inactivity, has indeed been detrimental in regards to attack rates. So I think there is a fairly substantial body of literature indicating that population groups which are regularly and physically active have benefitted.

I think what is not entirely clear is the magnitude of the exercise; in other words, how much is required. There is some difference of opinion in the literature about the degree of activity which seems to be preventive. So that we felt that this was by no means a closed issue, but that there was substantial evidence that regularly exercising populations seem to have lower attack rates.

DR. JENKINS: One addendum to Dr. Paul's excellent review would be the finding from the HIP study some years ago that not only did there seem to be lower attack rate among people who had either occupational or avocational exercise of moderate or heavy levels, but also the case fatality ratio was lower, suggesting some specific beneficial effect on the incidence on coronary death.

DR. FRANCES COHEN: I think that some of the comments that came out of our workshop involved the fact that pyschological and behavioral factors were thought to be considered very important in sudden cardiac death, in coronary heart disease in general, but that sometimes there were very strong methodological difficulties with the studies that had been done up to this point that made various people question those kinds of results.

There is a need for better studies to be done, with more methodological concern. It was agreed that the ideal type of study is a prospective study that looks at the important variables and follows them over time, and yet it is very difficult to get that type of research funded to include examining certain psychological factors. But yet it might be very useful to have some of those psychological variables looked at in ongoing prospective studies that have all the necessary and important cardiovascular information collected; it would be rather inexpensive to add psychosocial variables simultanesously to those kinds of studies.

At the same time, there are some ongoing longitudinal studies looking at psychosocial variables with psychological outcomes such as depression, and it might be possible for some cardiologists to work together with some of the more psychologically oriented people to include some of the variables that are necessary to simultaneously look at sudden cardiac death and heart disease in general as outcomes.

I think that after these kinds of studies are done--more sound studies that really look at a range of important variables--then we might have more positive things to conclude about the role of behavioral factors. But I don't think it is necessary to say that we can't study them, and that we need to look at all of the physiology first. We do really need to study them in a sound way, however, or we are just not going to be in a position to say anything strong about it.

THE FOLLOWING ARE EXCERPTS OF WRITTEN COMMENTS SUBMITTED BY WORKSHOP PARTICIPANTS AFTER THE CONFERENCE. THEY ARE INCLUDED TO SUPPLEMENT THE WORKSHOP SUMMARY.

Richard S. Ross:

I wonder whether there are any striking differences in the incidence of sudden death as an outcome of ischemic heart disease in radically different cultures. Obviously, we have data from Western European countries and Australia and there is no difference, but I wonder about China. Certainly, the whole attitude toward life, death, and illness is different. On my recent trip I visited a

large cardiac surgical center, the Fu Wai Hospital in Beijing. They have skilled cardiac surgeons and have done 13,000 open heart operations, but they do practically no coronary vein bypass procedures. When asked about this, they assured me that they had the expertise and had done ten, but that angina pectoris did not seem to bother the Chinese people enough to merit such a big procedure. Maybe it is attitude or environment or social background or conceivably a racial difference, but it would seem worthwhile to know whether sudden death is as common there as it is here. We have certainly learned a great deal about the eipdemiology of disease by looking at incidence in different cultures and trying to relate it to dietary habits, etc. This might be similarly rewarding.

William Ruberman:

As noted in the discussion, there is substantial agreement on the concept of sudden cardiac death. Such death is for the most part associated with underlying CHD, it is due to ventricular fibrillation; and ventricular arrhythmia -- often occurring long before the fatal event -- is an independent indicator of elevated risk. With this level of agreement on the end point, we can study its relation to factors such as defined categories of "psychosocial stress."

Studies in experimental animals are providing important evidence for the role of the CNS in modulating sensitivity to VF, both at the autonomic and higher-center levels. It is of particular interest that prior coronary artery occlusion and resultant electrical instability are necessary for the independent variable (drugs, autonomic interference, psychologically aversive environment) to achieve an effect.

The background of work on the clinical level that relates psychosocial stress to sudden death is less persuasive. There is evidence linking such stress to incidence of CHD and, to some degree, to CHD mortality, and thereby possibly to sudden cardiac death. However, studies linking behavioral paterns directly to sudden death are for the most part flawed by inadequate numbers, lack of controls, or faults in basic design. Our data at HIP on men with low education do suggest an elevated risk for sudden death, but only in men with complex VPB.

The animal and human data suggest that it is reasonable and practical to look first for links between biobehavioral factors and sudden death among patients with CHD and arrhythmia. Behavior modification to influence risk for CHD (diet, exercise, smoking, etc.) is currently in order, and if successful, should also reduce incidence of sudden death. At the current level of knowledge, it seems premature to speak of behavior modification specific for avoidance of <u>sudden</u> death.

Thomas P. Hackett:

One of the first questions that Dave Jenkins raised was whether or not the biobehavioral risk factors' contribution was large enough to make their reduction cost-effective in a public health setting. I would underline this question and say that one of my first priorities, as a result of this conference, would be to investigate ways of intervention in those factors which are known risks for conditions underlying sudden cardiac death. Since we know that smoking is one such risk factor, Type A behavior is another and exercise is perhaps a protecting factor I would tend to favor going after programs aimed at reducing risk through cessation of smoking, more healthful eating patterns, alteration of Type A behavior and encouraging exercise. Although there are many behavior modification programs afoot which have set out to do just this, my reading at this time is that none has been demonstrated to be particularly effective. In the realm of smoking, the MRFIT Program has the best cessation rate, but it is a long-term model, one that is not apt to be applicable to a large population. Since it is estimated that 95 percent of those individuals who have stopped smoking do so on their own without the aid of any of the known intervention programs, an examination might be made into the motives of those who have successfully quit on their own. However, I write this not so much to outline a type of research but to put my weight behind a program to go after the bird in hand, namely the known risks regarding cardiovascular disease. I would not spend much time investigating the possible predictors of factors that may be related to the acute phase of sudden cardiac death.

It was an interesting and profitable meeting. What it did for me was to underline how little we know about those factors correlating directly with the acute phase of sudden death and by contrast how much we know about the precursors of cardiovascular disease. What we don't know much about is how to change habits and personality traits to put them into a more healthy mode. That is the direction in which I would weigh the dice.

APPENDIX TO WORKSHOP A*

Behavioral Predictors of Sudden Cardiac Death: The Western Electric Study

The Western Electric study commenced in 1957, and was a long-term follow-up of a group of male employee volunteers (Paul et al, 1963; Ostfeld et al, 1964). The group consisted of 1878 previously healthy employees ranging from 40-55 years of age at the initiation of the study, whose annual health evaluation included assessment cardiac risk factors. Men who were discerned to have cardiac disease were excluded from the study at the onset. Each annual visit included a complete medical history, physical examination, chest x-ray, serum cholesterol determination (Abell-Kendall method), and ECG. The Minnesota Multiphasic Personality Inventory (MMPI) and other psychological questionnaires were administered the first year only. No attempt was made during these visits to prescribe diets or medication or to alter life style.

After ten years, comparisons were made between psychosocial factors at entrance into the study and subsequent development of cardiac disease. Psychosocial conditions on which the men had reported were: fatigue, due to causes other than excess physical activity; marked or moderate nervousness; former use of alcohol; and work tension, as determined by a positive response to an MMPI statement, "I work under a great deal of tension."

An individual's cardiac disease status was determined by the first clinically observable cardiac disease event during the ten years. These events were included in one of four categories: none (no event); sudden death; myocardial infarction; or angina pectoris. Chi Square testing was performed first on baseline frequencies for all four categories and then for a comparison of the three groups in which observable cardiac pathology had occurred (Table 1).

A large number of individuals describing themselves at baseline as "former drinkers" subsequently suffered sudden cardiac death within the ten year follow-up period. When compared to subjects not reporting this history, the group described as former drinkers had a relative risk of experiencing SCD six times that not reporting former drinking habits. (This can be calculated from the data presented in Table 1. Using the prevalence rates for each category, the number of

*Based on data provided by Dr. Richard Shekelle of Presbyterian-St. Luke's Medical Center, Chicago, IL, and Dr. Ogelsby Paul.

Table 1

Percentage Frequency of
Certain Psychosocial Conditions at Baseline

Conditions	None (1663)	Sudden Death (32)	Myocardial Infarction (83)	Angina Pectoris (100)	P-Values* All 4 Groups	P-Values* 3CHD Groups Only
Fatigue[1]	5.0	6.2	4.8	9.0	0.385	0.54
Nervousness (moderate or marked)	12.2	15.6	6.0	20.0	0.032	0.02
Former drinker	3.1	18.8	6.0	5.0	0.001	0.03
Work tension[2]	25.4	37.5	36.1	39.0	0.002	0.92

* P-Values based on the X^2 test

1. Reportedly due to causes other than excess physical activity.
2. A positive response to MMPI item 13, "I work under a great deal of tension."

former drinkers and nondrinkers can be calculated. The relative risk for drinkers or nondrinkers within a particular category can then be calculated by dividing that number by the total number of individuals sharing that psychosocial factor. For example, it is calculated that there probably were six former drinkers who experienced sudden cardiac death out of a total of 68 individuals who expressed this psychosocial factor. Thus,there probably were 26 individuals in this category who did not express that they were former drinkers. The calculated relative risks, therefore, are 8.8 for the former drinkers and 1.4 for those not expressing this characteristic, approximately a six-fold increase in risk for the former drinkers).

Among individuals reporting nervousness, significant differences were observed between those who did and did not subsequently have cardiac disease, as well as among those in the three cardiac disease categories; the highest reported frequency occurred in those who later developed angina pectoris. For those individuals reporting work tension, significant difference was noted for frequencies across all four categories, the lowest baseline rate occurring in the group with no cardiac pathology; no difference was observed among the three cardiac disease categories, however.

The mean values at baseline of a wider set of variables were also examined at ten year follow-up. The usual risk factors of age, cigarettes, systolic blood pressure, and serum cholesterol were apparent. Significant differences in mean values both between all four categories and among the three cardiac disease groups was observed for two baseline variables: MMPI depression scale and dietary cholesterol (mg/Kcal.). The mean MMPI depression scale score was highest for those in the sudden death category. Mean dietary cholesterol intake was also highest for those in the sudden death category, but mean serum cholesterol levels were not different from those observed for the other cardiac disease categories.

SUMMARY OF WORKSHOP B

BEHAVIORAL ISSUES IN THE ASSESSMENT, CONTINUING CARE AND REHABILITATION OF PATIENTS AT RISK FOR LIFE-THREATENING ARRHYTHMIAS*

CHAIR: Regis A. DeSilva
VICE-CHAIR: Joel Dimsdale

Participants: M. Cebelin, T. Dembrowski, R. Eliot, P. Frommer, J. Haft, W. Orr, P. Reich, D. Savage, T. Weiss

IOM Staff: D. L. Parron

This assembly of psychiatrists, psychologists, psychophysiologists, cardiologists and pathologists represents an attempt to discuss the clinical aspects of interactions between biobehavioral factors and sudden cardiac death. It is a timely effort because sudden cardiac death is the single most important health problem in the U.S. in terms of total numbers of deaths. Each day 1200 lives are claimed by SCD in the U.S.--almost one death per minute. This figure represents 60 percent of mortality due to coronary heart disease, making SCD the major mode of death in this condition. Sudden cardiac death finds its prime target among seemingly healthy males in their forties and fifties, thus the social and economic loss of men at their most productive phase of life is considerable. While for centuries man has been largely accepting of this outcome, it is becoming clear that deferment of sudden cardiac death is now a clinical possibility.

Basic Considerations

The nature of the lethal arrhythmia preceding death has been speculated upon since the 19th Century. McWilliam proposed in 1889 that ventricular fibrillation (VF) was the cause of sudden death. Other workers, principally Richter (1957), who studied rats forced to swim in water tanks, concluded that vagally-induced asystole was the

*Summary prepared by Drs. DeSilva and Dimsdale

essential mechanism. Wolf (1967) advanced this thesis and suggested that emotional stress evoked this atavistic "dive reflex" resulting in asystole with or without ventricular arrhythmias and sudden death. Contemporary out-of-hospital resuscitation studies, however, show that the most frequent cause of sudden death is ventricular fibrillation (Cobb et al, 1975). Asystole preceding death, when it occurs, is generally not psychologically mediated but rather is found as a terminal, irreversible rhythm in the presence of extensive cardiac damage following myocardial infarction. When heart block or asystole occurs during psychological and emotional stress, it mediates the simple faint which is self-limited with spontaneous recovery. Though it has been suggested that psychologically-induced and vagally mediated death occurs clinically (Engel, 1978), such deaths are probably unusual.

Victims of sudden cardiac death are most frequently found to have coronary artery disease at autopsy. A small fraction, perhaps 10-15 percent, have normal coronary arteries, with little or no evidence for structural heart disease. An even smaller proportion have cardiomyopathy, mitral valve prolapse and idiopathic hypertrophic subaortic stenosis (Savage et al, 1979).

Although coronary heart disease is the most important substrate for sudden cardiac death, it is known from epidemiologic studies that the major standard risk factors such as heredity, sex, hypertension, smoking, and hypercholesterolemia fail to discriminate between the person with coronary atherosclerosis and the future victim of sudden death (Gordon et al, 1977). In other words, the standard risk factors for both conditions are the same. What other risk factors, then, should be examined to explain sudden death in a patient who already has either silent or manifest heart disease? An attractive hypothesis is that in the patient with stable coronary arterial lesions additional factors deriving from outside the heart may provoke the lethal arrhythmia. One conceivable source for such factors is the activity of the central nervous system, which when aroused imparts transient risk to electrically unstable myocardium and precipitates ventricular fibrillation (Lown et al, 1977b; DeSilva and Lown, 1978a).

The clinical indictment of the central nervous system is not through direct evidence or by a preconceived conviction, but rather by exclusion when we consider the epidemiologic data and clinical observations over several decades. These observations compel closer examination of biobehavioral variables in sudden cardiac death. For the sake of completeness, in this discussion we are including not only "classical" behavioral attributes, but also the corollary biological events consisting of signaling within the central nervous system caused by neurochemical and psychophysiologic changes. These changes occur both in the conscious state and in altered states of consciousness with or without discrete or distinctly recognizable

behavioral patterns. Observations by researchers such as those of Eliot and colleagues (Eliot et al, 1977; Warheit, 1974; Reynolds, 1974) made on the space program community at Cape Canaveral, suggest that events such as loss of jobs and disruption of marital bonds were potent factors in provoking sudden cardiac death (Rahe et al, 1971, 1973, 1974; Parkes et al, 1969; Casscells et al, 1980) This type of information has been reviewed very well by the epidemiologic panel. It must be emphasized, however, that behavioral and psychological and emotional stresses, no matter how potent, are unlikely in and of themselves to precipitate sudden death. Two conditions are apparently necessary to bring about VF and sudden death:

(1) a vulnerable myocardium rendered electrically unstable and predisposed to VF usually because of coronary artery disease

(2) a superimposed psychological or psychobiologic event profound enough to precipitate the terminal arrhythmia. The clinical relevance of this concept is that VF may be viewed as an "electrical accident" which is a potentially reversible phenomenon. It should therefore form the major focus of our clinical endeavors. Furthermore, from preliminary data provided by cardiological groups around the country, it appears likely that sudden death due to VF is a pharmacologically preventable occurrence (Schaeffer et al, 1978; Lown et al, 1980b). The protection of the future victim is therefore a clinically realistic and attainable goal. It is necessary, in order to fashion an integrated approach to the problem, to consider the biobehavioral issues that appear to be involved in at least a subset of victims of sudden cardiac death.

Clinical Considerations

The clinical issues were reviewed very briefly: First, how do we identify the psychiatric and psychologic content that contributes to sudden cardiac death? Second, can we reproduce this setting in the laboratory, and how do we replicate studies to validate our hypotheses? Third, how is the neuro-effector sequence entrained and mediated physiologically? Fourth, what psychologic and psychiatric interventions are likely to yield benefit in managing the patient at risk for sudden cardiac death, and if the patient has already experienced sudden cardiac death on one occasion, how do we manage him or her subsequently? Finally, what neuropharmacologic approaches should be pursued to protect against sudden cardiac death?

We dealt systematically with each of these areas. In attempting to identify the psychologic and psychiatric contents in our patients lives, we recognize that the clinical tools are quite limited. Some insights about the settings in which sudden death occurs have been provided by interviews with relatives of the deceased and resuscitated victims. These studies have indicated that a certain percentage of cardiac deaths occur during acute emotional stress (Greene et al, 1972; Myers et al, 1975; Rissanen et al, 1978a, 1978b; Reich et al, 1981). Reich et al (1981) for example, showed that 21 percent of malignant arrhythmias (including VF) in 117 patients occurred under conditions of extreme emotional provocation or duress. The predominant affect was anger with agitation, fear, and grief admixed in some cases. These studies indicate that in some deaths, psychological and emotional factors may be of great importance in provoking sudden cardiac death, while in others, such factors seem to be of less importance.

Laboratory modelling of the candidate for sudden death or the resuscitated victim is very difficult insofar as biobehavioral factors are concerned. For one thing, it is not practical to induce and monitor the essential endpoint, i.e. ventricular fibrillation, in the laboratory. For another, it is virtually impossible to replicate and measure accurately in the laboratory the complex psychological and social setting in which SCD occurs. However, certain types of ventricular premature beats (VPBs) which are electrocardiographically recognizable, presage the onset of SCD. Such arrhythmias thus serve as a somatic target for assessing the effects of psychological stress, behavioral interventions and shifts of consciousness on the electrical properties of the heart in the future sudden cardiac death victim.

Psychological stress tests have shown that significant increases in VPB frequently occur during the stress period (Lown et al, 1978) Such tests are still very simplistic, may be irreproducible, and cannot be applied sucessfully to all patients at risk, because some patients will manifest no response. We need better tests that not only will identify the vulnerable patient, but also will demonstrate that behavioral interventions and an antiarrhythmic prophylactic program have been effective in containing the arrhythmia being treated. The clinical interview, combined with measures of physiological arousal such as changes in heart rate, blood pressure, and forearm blood flow may yield a profile of candidates at risk for sudden death. These studies would parallel those of Dembrowski et al (1978) and Glass et al (1980) in which a statistical link was established between the Type A coronary-prone pattern and enhanced cardiovascular and catecholamine response to laboratory-based social psychological challenges involving mental and/or psychomotor skills. Patterning of the neuro-endocrine and physiological responses may make it possible in the future to develop diagnostic procedures for the identification

of a subset of patients susceptible to SCD. Furthermore, if this approach proves fruitful, laboratory paradigms of this type may be used to determine the sort of pharmacologic and behavioral interventions that can be used to alter physiologic reactivity and perhaps reduce the possibility of cardiac death. It must be emphasized that such research is still in its infancy at this stage. Preliminary studies already suggest that "joyless striving" and depression states may be associated with ventricular arrhythmias and sudden death (Bruhn et al, 1974; Orth-Gomer et al, 1980).

The next issue we dealt with was the neuroeffector sequence that is entrained during psychological stress. There is a need for greater clarification of the intermediary mechanisms, both neurohumoral and pathophysiologic, because there still is a very large gap in knowledge between the putative psychologic stress and the end-result of ventricular fibrillation.

Biochemical intermediaries of the pathophysiologic response to stress need to be examined in detail. A number of investigators have already examined the role of catecholamines in relation to stress-induced cardiovascular changes. Although both epinephrine and norepinephrine increase in the context of anxiety, the plasma epinephrine response to anxiety is much more pulsatile, manifesting dramatic swings (Dimsdale et al, 1980) The fact that propranolol, a beta-blocker, has sometimes been effective in treating arrhythmias induced in a setting of emotional arousal suggests that epinephrine may be a link between anxiety and arrhythmias. Nevertheless, it must be emphasized that there is negligible direct information about the association of plasma catecholamines and arrhythmias. Simultaneous observations of cardiac rhythm by Holter monitoring and withdrawal of blood catecholamines over a period of psychological stress will be a useful method of study (Dimsdale et al, 1980). It already appears that catecholamine-induced arrhythmias may exist as suggested by Conmel et al (1978). The most striking clinical example demonstrating the link between emotional states, sympathetic neural discharge and malignant arrhythmias is the prolonged Q-T interval syndrome (Wellens et al, 1972) Observations made on patients with this syndrome suggest a strong and valid link between the central nervous system and the provocation of VF. There is little information on the role of corticosteroids in sudden cardiac death. If the depression and the "giving up" reaction is of relevance to sudden cardiac death, then it would be valuable to determine the changes in steroid hormone levels which occur in response to psychological stress (Troxler et al, 1977)

We have to examine issues related to coronary vasoreactivity and coronary spasm. Coronary spasm is thought to be mediated by vasoactive amines, as well as directly by the neural innervation to the heart. This area of cardiology and psychophysiology has been incompletely studied in relation to psychobiologic variables. It is

known, for example, that psychologic conditioning and stress in animals can produce changes in the coronary vascular bed with alterations in coronary blood flow. Reflex spasm of the coronary vascular bed also occurs in patients with ischemic heart disease by activation of alpha adrenergic receptors (Mudge et al, 1976a, 1976b). Induction of such transient alterations in coronary blood flow may result in ischemia and trigger malignant arrhythmias. Activation of coronary neural innervation by behaviorally related stimuli probably occurs in man and the delineation of this relationship awaits exploration.

Clinical studies have shown that sudden death victims with coronary artery disease may demonstrate increased frequency and size of platelet aggregates in coronary vessels (Haerem 1971). Activation of the adrenergic system during stress responses also results in alterations in platelet physiology and is in part related to release of catecholamines, thromboxane, prostaglandins, thrombin, serontonin, and fatty acids, all of which induce platelet aggregation (Harker et al, 1980). Pathological studies have shown platelet aggregates in epicardial and intramyocardial vessels of patients dying suddenly and unexpectedly. Experimental studies have shown that intracoronary injection of adenosine diphosphate (ADP) and norepinepherine in dogs results in platelet plugs (Haft et al, 1972) Such plugs may conceivably further obstruct narrowed coronary arteries and result in myocardial infarction or ventricular fibrillation.

Psychological stress in animals subjected to electrical shock and heat results in platelet plugs in coronary arteries, myocardial necrosis, and hemorrhages (Haft et al, 1973). Whether this occurs in human beings has yet to be demonstrated, but it is known that stress, e.g. before surgery, may result in increased platelet aggregation (Fleischman et al, 1976). Antiplatelet drugs such as aspirin, dipyridamole, and clofibrate (Haft et al, 1972a) protect against myocardial damage resulting from platelet aggregates. Clinically, such antiplatelet substances are being investigated as agents to protect against acute coronary events (Elwood et al, 1980; Anturane Reinfarction Trial, 1978; Persantine-Aspirin Reinfarction Study, 1980). It is likely that behaviorally activated platelet aggregation and the release of various biochemically active substances result in changes in blood flow, myocardial damage, and ventricular arrhythmias leading to sudden death. These changes may be prevented by anti-platelet substances.

The cardiac effects of the pathological and physiological alterations induced by psychological stress have been documented in a few animal and human studies. Microscopic pathological changes of necrosis, contraction bands in heart muscle, and empty sarcolemma sheaths have been seen in victims of sudden death; these are similar

to the changes seen in catecholamine-induced myopathy (Baroldi, 1979; Eliot, 1978). Cebelin and Hirsch (1980) have shown that sudden death in victims of attempted homicide may be due to cardiac degeneration engendered by acutely stressful situations. Microscopic lesions of myofibrillar degeneration are similar to those occurring after prolonged infusions with catecholamines and in patients with pheochromocytoma. Presumably, these victims who died suddenly succumbed to a malignant ventricular arrhythmia.

We have to determine what psychologic and psychiatric interventions we can use to manage the patient at risk for sudden death and to deal with patients who have been resuscitated from sudden death. The roles of meditation biofeedback and sleep may be relevant in this regard (DeSilva et al, 1978a; Weiss et al, 1971; Benson et al, 1978; Pickering et al, 1977b; Voukijdis et al, 1977; Cheatle and Weiss, in press). Non-cult forms of meditation and biofeedback have shown that significant changes in ventricular arrhythmia frequency can be attained (Weiss, 1971; Benson, 1975). However, the results of meditation and biofeedback are variable and there is no certainty about the long-term effects and benefits of these procedures on cardiac arrhythmias. Preliminary data from Weiss (unpublished observation) indicates that adaptation or placebo effects may account for much of the VPB frequency reduction seen.

Studies of the effects of sleep on cardiac rhythm provide insights into the effects of CNS activity on electrical properties of the heart and further elucidates the neural mechanisms that may be involved. Some studies have shown that there is little or no effect of sleep on cardiac rhythm between various stages, but others suggest an increase in VPB frequency during shifts from one sleep stage to another (Rosenblatt et al, 1969; Lester et al, 1969; Smith et al, 1972; Orr et al, 1979). Other workers have speculated that REM sleep may trigger fatal arrhythmias and that a hazardous "REM rebound" after withdrawal of hypnotic medications may occur (Orr, 1975). However, studies conducted in larger populations have shown that, in patients who were largely unmedicated and were not studied in the coronary care unit, sleep had an antiarrhythmic effect (Lown et al, 1973a; DeSilva et al, unpublished observations; Pickering et al, 1977, 1978). Stages I to IV sleep had the most marked antiarrhythmic effect, while VPB frequency during REM sleep was the same as during the awake state (DeSilva et al, unpubished observations). These effects are very likely due to reduction in sympathetic neural tone and increase in vagal tone (except during REM sleep) that occurs during sleep. Sleep deprivation and fatigue, though unstudied, may be important in engendering fatal arrhythmia, because it is reasonable to assume that these conditions may further destablize the already electrically unstable heart.

What newer pharmacologic approaches are there to sudden cardiac death as it relates to emotional and neural triggering of

arrhythmia? This is a new area of research. The focus of some investigations has been to look at alterations in central neurotransmitter function. In animal models it has been found that alterations in serotonin and in dopaminergic mechanisms in the brain were able to protect the heart against electrically-induced ventricular arrhythmias. Specifically, research has been targeted on the amino acid precursors of central neurotransmitters such as tryptophan, the precursor of serotonin; and tyrosine, the precursor for norepinephrine, epinephrine and dopamine (Rabinowitz et al, 1978; Scott et al, 1981a). The roles of beta-endorphins and enkephalins in regard to the cardiovascular system need study and application in therapy if appropriate.

Bigger, Glassman, and their coworkers (1977) have examined the effects of centrally acting tricyclic antidepressants to subdue ventricular arrhythmias. No doubt these agents affect catecholamine release and reuptake in the brain and influence other neurotransmitters which affect cardiac electrical properties. It is likely that, in selected subsets of patients who are susceptible to emotionally and neurally triggered arrhythmias, such centrally acting drugs may be useful for adjunctive management.

Clinical Management and Psychosocial Interventions

Although questions of clinical management are implicit in much of the foregoing discussion, they should be addressed directly. In particular, the following require emphasis: (1) the importance of educating spouse and the family of resuscitated and "at-risk" patients about the disease process and about techniques of cardiopulmonary resuscitation; (2) the careful search for relevant psychological precipitants for arrhythmia in the resuscitated patient. Such a search, when conducted with simultaneous Holter monitoring, interviews, and observations of the patient at home with the family or in the work setting, may provide important information for managing the individual patient. Such mangement suggestions may be directed at pharmacological intervention, lifestyle modification, or psychotherapy. While none of these management dispositions is likely to be quick and uniformly effective, one must consider the alternative and recognize that the clinical management of these patients, even if limited primarily to antiarrhythmic drugs, is also a time-consuming process. It is hoped that prevention can extend beyond these tertiary prevention possibilities to methods of prospectively identifying individuals at risk for behaviorally activated sudden death and facilitating appropriate interventions or alterations of lifestyle.

Despite deficiences in research methodology in areas such as these (Aitken, 1973) the issues we have raised must be addressed.

Clinical investigation and management of arrhythmia patients require interdisciplinary cooperation. Collaborative investigations among cardiologists, psychiatrists, and behaviorists may yield new strategies for management.

Conclusion

Medical history is replete with examples of successful therapies being found long before the diseases were understood. We can proceed to deal with the clinical problems of sudden cardiac death before we fully work out details of the role of the central nervous system in provoking ventricular electrical instability and ventricular fibrillation.

Although death is the ultimate outcome of coronary atherosclerosis, extended deferment of sudden death is possible. If the resuscitated victim is carefully managed, a productive life is possible. The goal is to predict the premature onset of sudden death and to fashion a program to avert it.

THE FOLLOWING ARE EXCERPTS OF WRITTEN COMMENTS SUBMITTED BY WORKSHOP PARTICIPANTS AFTER THE CONFERENCE. THEY ARE INCLUDED TO SUPPLEMENT THE WORKSHOP SUMMARY.

Robert S. Eliot:

I would like to make the following comments with regard to Workshop B, 'Biobehavioral Issues in the Assessment, Continuing Care, and Rehabilitation of Patients at Risk for Life-Threatening Arrhythmias.'

First, the evidence which we and others have presented indicates that there clearly is a link between the central nervous system and myocardial necrosis, both in man and in experimental animals. In some instances these links (coagulative myocytolysis) can be prevented by pre-treating animals with beta blockers. Obviously, many other pathophysiologic studies exist that point to the powerful relationship between the central nervous system, its interpretation of events, and its expression of these events in physiologic, metabolic, and ultimately pathological states.

Second, utilization of psychophysiological testing is a great asset in that it allows us to communicate with traditional medical fields in physiologic terms. This common language, understood throughout the fields of medicine, is able to measure the rate at

which a given parameter changes, the duration of these changes, and the rate of return to the resting level. Beyond rhythm disturbances, it is important to keep in mind other significant hemodynamic measurements that can offer the measurement of stress through its hemodynamic component of strain. Indeed, through non invasive systems it is possible to measure myocardial oxygen consumption, the work of the heart, total systemic resistance, and a variety of other key hemodynamic factors, and to gather a valid data base.

Obviously, it will be important that there be some standardization of this type of study in order that as time goes by there will be a large enough experience to offer some indication of the sensitivity, selectivity, and ultimately the prognostic value of these forms of assessment. One of the functions of the Academy could indeed be the maintenance of a research group oriented toward the study of psychophysiological testing as a research, and ultimately as a service tool.

Redford B. Williams:

Since a strong case can be made for the participation of acute increases in sympathetic nervous activity in the precipitation of sudden cardiac death (SCD) in humans, and, since it is clear that certain behaviors (e.g., mental work) and emotions (e.g., anger) are associated with increased sympathetic discharge, the role of such behaviorally/emotionally-induced sympathetic activity in SCD might be evaluated in a controlled clinical trial of behavioral training to reduce sympathetic discharge in such situations. Since persons with known coronary disease constitute the population at risk for SCD, a random sample of such patients could be treated using a stress management approach designed to teach them how to relax and hence reduce sympathetic activity during stressful life situations. A second random sample would receive regular medical care and constitute a no treatment control group. If the incidence of SCD were found to be significantly reduced in the stress management group compared to the control group, then the case for an etiologic role of behavioral factors in SCD would be strengthened. At the same time, a potentially effective intervention would have been identified. Such an approach is entirely analogous to the clinical trials of propanolol in post-myocardial infarction (MI) patients. Meyer Friedman is conducting just such a study of behavior therapy in Type A post-MI patients at the present time, and preliminary results suggest that this approach is indeed associated with a significant reduction in mortality in the first year post-MI.

... It appears to me that one useful approach would be the 'add-on' of behavioral science components to other ongoing or planned biomedical projects. The clinical trial of stress

management to reduce SCD described above is an example. The assessment of Type A behavior pattern in the MRFIT program is another. All over the country there are currently being followed large cohorts of patients with coronary disease who have been characterized in terms of sophisticated measures of coronary anatomy and cardiac function. In a paper to be presented at the upcoming annual scientific sessions of the American Heart Association, we report that hypochondriasis and hysteria scores on the MMPI are better predictors of pain relief with either surgical or medical management in coronary patients than any physical characteristic. Therefore, it would be well to begin collecting such psychosocial data in the above mentioned cohorts, so that the role of behavioral factors in the various outcomes of interest (pain relief and survival) could be documented, with the eventual goal of using such information in the process of treatment selection. Identification of psychosocial characteristics that are predictive of poor outcome could lead to selection of high risk groups for specific intervention employing behavioral treatment approaches.

Peter Reich:

I doubt whether there is a clear separation between those patients who are susceptible to psychological disturbances and those who are not. ... We have been more impressed by the synergism of various destabilizing influences that together create the conditions that uniquely trigger an arrhythmia, while taken separately each would have been benign. There may be a <u>few</u> patients who have an excessive degree of responsiveness to certain psychological situations and, of course, there are those patients who have SCD in the midst of an overwhelming psychophysiological catastrophe.

In general, I believe the conference suffered from the emphasis on the entire sudden death syndrome. This led to the frequently repeated concept of heterogeneity. A few referred to the specific problem of the ambulatory, relatively healthy patient who dies suddenly without having had a myocardial infarct -- a group that constitutes two-thirds of the out-of-hospital sudden deaths in the Seattle studies. I doubt whether vagal asystole is a significant contributor to this sizeable subgroup. These patients really constitute the crux of the problem.

How to go about stimulating relevant research is a difficult question. I found the conference extremely stimulating and carried away a number of ideas on the psychological stress test issue. My impression at the conference was that very few of the participants were really seeing sudden death victims. I think the problem is still at a level where continued contact with sudden death victims who have survived will be necessary for creative research.

SUMMARY OF WORKSHOP C

BIOBEHAVIORAL ELEMENTS IN THE PATHOPHYSIOLOGY OF SUDDEN CARDIAC DEATH*

CHAIR: J. Alan Herd
VICE-CHAIR: R. Verrier

Participants: J. Buell, D. Cohen, L. Cohen, J. Dingell, J. Henry, J. Lacey J. Lawler, R. Randall, D. Reis, C. Spielberger, R. Williams

IOM Staff: G. Elliott

The task of Workshop C was to discuss biobehavioral elements in the pathophysiology of sudden cardiac death. We focused primarily on needs and opportunities in animal studies and clinical research, dividing our attention among three main topics--heart, brain, and behavior. In each of these topics, we sought to appraise the current knowledge, to highlight promising avenues suggested by existing research, and to predict where studies might lead in the future and what technologies might lend themselves to the most rapid advance. We also tried to identify special needs, such as desirable technological advances, changes in the organizational structure in which research is done, and matters that appear not to have received appropriate amounts of attention to date.

Cardiac Aspects

Animal and clinical research provide several insights into the contribution of the heart to sudden cardiac death. First, for sudden cardiac death to occur, the heart must have some type of predisposing condition. The great majority of sudden cardiac deaths are associated with ischemic heart disease (Lown, 1979). Other potential risk factors are pharmacological agents, such as diuretics and digitalis, and environmental toxins, such as fluorocarbons and carbon monoxide. These factors seem to have in common the induction of imbalance among action potentials. There is a segmental dissonance of electrical activity among different parts of the ventricle and perhaps some threshold reduction or increased

*Summary prepared by Dr. Herd and Dr. Glen Elliott

susceptibility of individual fibers to stimulation, as well as an imbalance of threshold and duration of action potentials among regions (Han et al, 1964).

A particularly promising animal model for sudden cardiac death entails a combination of cardiac ischemia and altered neuronal input through direct stimulation to the heart, brain stimulation, or conditioning procedures. This model already has provided much useful information, as discussed more fully by Dr. Verrier.*

Cardiac physiologists have clarified many of the regulatory mechanisms for electrical activity of the heart (Randall et al, 1977; Schwartz et al, 1978). Pump function is reasonably well understood; and a great deal is known about metabolic, chemical, and neuronal influences of cardiac performance. Also, much has been learned about the mechanisms that control coronary blood flow.

More information about the heart is a requisite component of efforts to understand how behavior influences the phenomenon of sudden cardiac death. Our workshop identified several areas that seem particularly promising for future research. What are the specific acute and chronic effects of myocardial damage--whether it be ischemic, chemical, or metabolic-- on electrical activity? We recommend a special focus on the effects of myocardial damage on afferent and efferent innervation of the heart. How does damage alter receptor density and sensitivity? Are there meaningful regional variations? What is the temporal pattern of such changes? How do they affect myocardial performance? Do they alter myocardial sensitivity to other influences, including plasma catecholamines? We also urge continued support of efforts to gain a better understanding of cardiac innervation and of cardiovascular reflex responses. For example, how does myocardial damage change the influence of arterial baroreceptors on cardiac response to nerve and endocrine stimulation?

Controls of coronary blood flow also are important. More information is needed about neuronal pathways that mediate psychosocial and behavioral-induced changes in coronary blood flow. Particularly useful would be animal models that have predisposing elements involving coronary pathology. Perhaps coronary artery disease, for example, arteriosclerosis induced by nutritional interventions, might serve this purpose.

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* See presentation by R. Verrier, pages 57-69.

Neuroregulatory Aspects

Consideration of behavioral influences on sudden sudden cardiac death requires attention to brain physiology and chemistry. There has been a surge of new information recently about neuroregulators and about neuronal pathways in the brain. For example, anatomical connections and electrical characteristics of pathways associated with vision have been mapped. The neurochemical substrates of this and other systems has been more difficult to establish unequivocally. However, the advent of new technologies and new discoveries in this field promises a rapid expansion of knowledge about neuroregulatory mechanisms over the next few years (Barchas et al, 1978). With regard to neuronal influences on the heart, considerable information already is available about relevant systems in the brainstem, spinal cord, and peripheral organs, such the heart and the adrenal medulla (Cohen et al, 1979). The important roles of acetylcholine and of the catecholamines norepinephrine and epinephrine have been appreciated for years. It remains to be learned how their roles are augmented or modified by more recently discovered neuroregulators such as the neuropeptides. Particularly important will be efforts to learn how neuroregulators affect the electrical function of the heart and coronary blood flow in ways that may predispose to or protect from sudden cardiac death.

We identified several critical directions for research on the central nervous system control of cardiovascular function. Investigators already have shown that the brain innervates the heart directly and that direct stimulation of some parts of the brain increases activity of those nerve pathways, producing changes in cardiac function. How do various systems linking brain with heart actually function under normal conditions, and how do such functions change following cardiac damage? What are the precise anatomy and physiological purpose of these pathways? The technologies being developed to study neuroregulators in the brain should be directly applicable to answering such questions.

We concluded that central nervous system regulation of the autonomic nervous system is of general interest. In addition, a conception of the role of this system in cardiovascular control may be key to understanding sudden cardiac death. For example, the direct actions of the sympathetic and parasympathetic nervous systems on the heart are of obvious importance. How important are other effects, such as those on vascular resistance and cardiovascular load to cardiac function and pathology?

Much of the future research in aspects of sudden cardiac death will have to be interdisciplinary. Efforts such as described in this conference are needed to foster interactions among scientists who know how to interpret and to alter behaviors and their psychological attributes, as well as those who can measure and

manipulate chemical and electrophysiological components of the brain. Investigators have only begun to tackle these complexities, and little of the work done to date is directly relevant to cardiac malfunction. How do various psychological states alter cardiac function? Through what mechanisms? Can cardiac disease interrupt critical reflex arcs? How can such reflexes be identified, and what changes them?

Behavioral Aspects

As discussed in the plenary presentations at this conference, clinical and animal studies strongly confirm that behavior can be a significant contributing factor to sudden cardiac death. In many ways, this is the single most important conclusion to be drawn from existing data. Still, major questions remain. Is there any specificity? Are effects acute and transient or chronic and cumulative? Some patterns of interactions with the environment may influence the development of physiological risk factors for sudden cardiac death; others may precipitate sudden cardiac death in susceptible individuals. For example, the neuroendocrine changes associated with strong emotions may be associated with acceleration of atherosclerosis, which may in turn damage the heart in ways that make it vulnerable. In someone at risk, an acute event may produce changes in hormonal or neuronal activity that result in sudden cardiac death. Is it possible to distinguish reliably between emotional states or personality traits that predispose to sudden cardiac death and events that precipitate it? Advances in developing state-trait measures of anxiety and anger and the demonstrated importance of the Type A behavior pattern as a risk factor for coronary heart disease indicate the feasibility of doing good research on these questions.

There appear to be characteristic physiological patterns of cardiac electrical, neuroendocrine, and hemodynamic responses to different behavioral states such as defense, novelty, and the diving reflex (Eliot, 1979; Cohen, 1975; Wolf, 1969). In general, a limited number of distinct patterns have been observed, but these may manifest themselves in complex combinations. What are the short- and long-term consequences of these responses on the heart? Which ones most often precipitate sudden cardiac death? Can they be modified with conditioning? Do some response patterns suppress potentially lethal responses? Can those be augmented or consciously induced? Studies of the biochemical and neurophysiological metabolic events that accompany intense emotional states such as anger or anxiety also are urgently needed, especially in human beings.

Both animal and human research will be necessary to clarify the precise role of behavioral and psychosocial factors in sudden

cardiac death. Do certain pre-existing behavioral traits increase the likelihood that such events will occur or sensitize an individual to them when they do occur? What role do control over and predictability of environmental events play? What mechanisms underlie the ability of these psychosocial factors to augment or alter physiological responses in ways that predispose to sudden cardiac death or precipitate it? Better animal analogues are an especially pressing need. In humans, retrospective studies of survivors of sudden cardiac death episodes or of acute myocardial infarction have been and will continue to be important techniques for exploring the behavioral and emotional components to sudden cardiac death. However, prospective studies also are crucial, because they help to avoid biases inherent in retrospective studies. Such large-scale studies are expensive, therefore they should employ the best available measures for distinguishing emotional and cognitive (subjective) from behavioral (objective) factors.

In clinical studies, we identified a need for broader psychological assessment, with special efforts to provide objective quantitation of the variables being measured, particularly along such emotional dimensions as anxiety and anger. In too many cases, interesting data about victims of sudden cardiac death lose much of their value because appropriate controls and test standardization are lacking. How do healthy people and those with problems other than sudden cardiac death compare to the study population along such dimensions as acute stressful events, personality traits, and chronic conditions? How do people who die from sudden cardiac death differ from others in terms of personality traits, chronic conditions, or recent acute stressful events? How do they differ along social and cultural dimensions? Do recent changes in life styles account for a recently observed decrease in subacute cardiac death? If so, which ones are important? Can we encourage others who are at risk to make similar changes?

Summary

The evidence warrants the following conclusions. First, sudden death occurs in a susceptible heart. Predisposing conditions may include ischemia, conduction abnormalities, or chemical imbalances. Such potential risk factors need to be identified more precisely. Second, pathways exist by which the brain can influence cardiac function. Third, a triggering event often seems to be involved in sudden cardiac death. Together, the susceptible heart, the regulatory pathways, and the triggering event combine in some individuals to produce sudden cardiac death. At present, investigators usually have been able only to identify a string of plausible links among these three factors. The participants in this workshop concluded that the time is right to pursue each in more

depth and to encourage collaborative efforts designed to clarify their interrelationships.

ADDENDUM TO SUMMARY OF WORKSHOP C: BIOBEHAVIORAL ELEMENTS IN THE PATHOPHYSIOLOGY OF SUDDEN CARDIAC DEATH

RICHARD VERRIER (Workshop Vice-Chair): As Dr. Herd's summary indicated, there are many unanswered questions regarding the role of behavioral factors in the provocation of sudden cardiac death. Unfortunately, the time required to pursue all the issues would be enormous and the cost prohibitive. The major challenge, then, is to select the crucial questions and attempt to leap-frog whenever possible. The following are some specific questions.

One of the most pressing problem areas is the improvement of biobehavioral models. While experimentalists can never hope to replicate the entire spectrum of human emotions, some guidelines from clinical investigations are available. For example, in patients with identifiable psychologic disturbances preceding malignant ventricular arrhythmias, the most common affective state observed was anger (Lown et al, 1980; Verrier et al, 1981). Thus, in animal studies it would seem logical to focus on aversive paradigms designed to stimulate an anger-like state.

Sleep is another pertinent behavioral state which has not been adequately studied. Both sleep and sleep deprivation are amenable to modeling in the research laboratory (Lown et al, 1973a; Skinner et al, 1975b).

On the mapping of neural pathways, experimental and clinical evidence indicates that investigative efforts should be concentrated on the sympathetic limb of the autonomic nervous system (Lown et al 1980; Verrier et al, 1981). The potential for therapy through neurophysiologic intervention is clearly illustrated in the long Q-T syndrome (Schwartz, 1980). In many of these patients surgical ablation of peripheral sympathetic ganglia of pharmacologically induced beta-adrenoreceptor blockade can prevent recurrence of malignant cardiac arrhythmias (Schwartz, 1980). It is worth considering the possibility that interruption of the sympathetic nervous system may protect against sudden cardiac death due to other etiologies, including ischemic heart disease.

In light of growing clinical evidence implicating coronary spasm in the genesis of cardiac arrhythmias (Masseri et al, 1980; Hillis and Braunwald, 1980), the possibility that behavioral stress may result in inappropriate coronary vasoconstriction should be explored. Indeed, the coronary vessels are richly innervated and

intense coronary artery vasoconstriction can be induced by adrenergic stimulation in animals (Vatner et al, 1974) and humans (Mudge et al, 1976b). If inappropriate coronary vasoconstriction was implicated in the provocation of cardiac arrhythmias during behavioral stress, an effective armamentarium of coronary dilators could be drawn upon.

These observations lead naturally to the suggestion that it is not too early to turn to preventive measures, rather than to continue to reiterate the interesting but potentially self-limiting theme that certain psychologic factors may trigger ventricular fibrillation. How can we protect the heart by neurobiologic intervention? What is the appropriate therapeutic role of pharmacologic or surgical blockade of the autonomic nervous system? Can sedative medications be employed effectively? Would dietary changes alter central neuroendocrine function sufficiently to afford any beneficial effects? These and other possibilities seem to be highly promising and merit vigorous pursuit.

EXCERPTS OF WRITTEN COMMENTS WERE SUBMITTED BY WORKSHOP PARTICIPANTS AFTER THE CONFERENCE. THEY ARE INCLUDED TO SUPPLEMENT THE WORKSHOP SUMMARY.

RICHARD S. ROSS:

If the coronary arteries can go into spasm, what about the cerebral arteries? Is it possible that cerebral vascular spasm produces ischemia in a certain part of the brain, which in turn triggers a spasm in the coronary arteries?

It seems to me that the time is right to make big strides in the whole field of behavior and physiology. Within the last decade it has been possible to measure blood flow, nerve traffic, and the concentrations of neurotransmitters. The psychological techniques for producing stress in animals have improved and it is now possible to study conscious animals. It seems to me that with the tools we have now and the good animal models we ought to make a lot of progress.

DAVID C. RANDALL:

Dr. Herd's summary clearly identifies a considerable number of research questions which remain to be answered. However, it also stresses that there is a large body of basic physiological and behavioral knowledge from which to work. One of my concerns in reviewing the literature is that this background is not being

adequately exploited. This may be a particular problem in a multidisciplinary undertaking, but in many cases may be avoided by fertile collaborative efforts. Physiologists are, I'm afraid, particularly prone to have very poor behavioral controls in their experiments. They also tend to have rather haphazard experimental designs. Likewise, behaviorists tend to get minimal physiological data from their elaborately designed and conducted experiments. As a physiologist I am discouraged that potent, provocative experimental data and concepts already available are often left unused in attacking the problem of sudden cardiac death.

Many, perhaps most, of us have been principally interested in a single organ, and may even have devoted our research to a specific aspect of the function of that organ. However, the problems of the biological and behavioral bases of sudden cardiac death, and probably many other disease states, require a much broader 'systems' approach to their solution. Unfortunately, our educational and research programs are not oriented in this direction, and it may take a major effort to induce the necessary changes. However, there are already a number of individuals and programs which might have valuable insight into how one should approach research of this nature. Perhaps a limited effort aimed at giving their ideas broader circulation to investigators interested in 'bio-behavioral' questions would be valuable?

JAMES E. LAWLER:

Most of us tend to use one ill-defined word, 'stress', when speaking of biobehavioral factors. It is a word which is obviously applied to many different situations. What is more, it is a term appled to situations which lead to drastically different physiological responses. We tend to use stess as a unitary concept. We need to emphasize that certain patterns of interacting with the environment may be more conducive to SCD than others. Certain situations may be more conducive to eliciting a pre-fibrillatory behavioral response. For example, behavioral paradigms which require animals to exert some control over their environment, while still maintaining some degree of unpredictability or uncontrollability, may optimize physiological responses conducive to SCD.

CHARLES D. SPIELBERGER:

My comments relate primarily to the empirical, theoretical, and epistemological issues which I noted during our second workshop session.

It is important to distinguish between feelings (emotional reactions), cognitive processes, and behavior. While there is as

yet little evidence of how differences in these phenomena contribute to sudden cardiac death, there is growing evidence that anger and hostility are important factors in myocardial infarction, and that anger and anxiety play a role in the etiology of hypertension.

[In this workshop summary,] 'behavior,' seems to refer rather ambiguously to feelings, cognitions and behavioral reactions. I believe that it is critical to distinguish between emotional states (feelings) and associated thoughts and ideas (cognitions), and their manifestations in behavioral reactions. For example, the data that I briefly referred to in our workshop suggested that hypertensive patients frequently experience intense anger, which they tend to suppress. It is important to study the intensity of an individual's feelings (emotional states) and the frequency that such feelings are experienced (traits), as well as manifestations of feelings in behavior.

... Promising state-trait measures of anxiety and anger, and of the Type A behavior pattern, have been developed over the past decade, and such measures should be employed in research on sudden cardiac death and other forms of heart disease where possible.

I certainly agree that animal analogues to sudden cardiac death are urgently needed, and the case for prospective studies should be made stronger by noting that 'prospective studies are <u>even more crucial</u> to avoid biases inherent in retrospective studies.' I would also like to add that studies of the biochemical and neurophysiological metabolic processes that occur during intense states of anger and anxiety are urgently needed, especially in humans.

...We need to learn more about the neural and biochemical processes that mediate the possible influence of negative emotional reactions such as anger and fear on sudden cardiac death.

... It might be noted, for example, that anger and anxiety are the internal states that appear to mediate Cannon's fight or flight reactions. The consequences of arousing these strong emotions, and the neuroendocrine reactions associated with them, may lead to circulation of biochemical substances in the bloodstream to support these emergency reactions that cannot be utilized because of the social constraints of modern society.

... Personality traits should be included both among the 'predisposing conditions' and the 'triggering events.' There is growing evidence that anger and hostility are associated with atherosclerosis and the <u>frequent</u> experience of <u>intense</u> anger which is suppressed or only partially expressed appears to contribute to hypertension. Therefore, the contributions of these factors to sudden coronary death should be carefully evaluated.

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CONFERENCE AGENDA

BIOBEHAVIORAL FACTORS IN SUDDEN CARDIAC DEATH

Peter B. Dews, M.B., Ch.B., Ph.D., Chair

Tuesday, August 5, 1980

Plenary Meeting - NAS Auditorium

9:30	Welcome and Orientation to "Health and Behavior: A Research Agenda"	Judith Rodin, Ph.D.
9:35	Introductory Remarks: The Public Health Burden of Sudden Cardiac Death	Peter Frommer, M.D.
9:45	The Clinical and Pathological Syndromes of Sudden Cardiac Death: An Overview	James Buell, M.D.
10:00	The Role of Coronary Artery Spasms in Life-Threatening Arrhythmias and Sudden Cardiac Death	Eugene Braunwald, M.D.
10:15	Comment on the Classification of Sudden Cardiac Death	Lawrence Hinkle, M.D.
10:20	Discussion from the Floor	
10:50	Coffee Break - NAS Great Hall	
11:05	Experimental Studies of Psycho-physiological Factors in Sudden Cardiac Death	Richard Verrier, Ph.D.
11:35	Toward a Cardiovascular Neurobiology	David Cohen, Ph.D.
12:00	Discussion from the Floor	
12:30	Lunch - NAS Refectory	
1:30	Behavioral Risk Factors for Sudden Cardiac Death	David Jenkins, Ph.D.
2:00	Clinical Observations on the Psychobiology of Life-Threatening Dysrhythmias	Peter Reich, M.D.

Tuesday, August 5, 1980 (continued)

2:30	Opening Discussant	William Greene, M.D.
2:40	Discussion from the Floor	
3:30	Closing Discussants	Robert Eliot, M.D. Lawrence Hinkle, M.D.

Workshops

4:00	Workshop A: Prevention of Sudden Cardiac Death: Identifying, Understanding, and Modifying Behavioral Risk Factors	Chair: C.D. Jenkins, Ph.D. Vice-Chair: O. Paul, M.D.
	Workshop B: Biobehavioral Issues in the Assessment, Continuing Care, and Rehabilitation of Patients at Risk for Life-Threatening Dysrhythmias	Chair: R. DeSilva, M.D. Vice-Chair: J. Dimsdale, M.D.
	Workshop C: Biobehavioral Elements in the Pathophysiology of Sudden Cardiac Death	Chair: J.A. Herd, M.D. Vice-Chair: R. Verrier, Ph.D.
5:30	Cocktails - NAS Great Hall	

Wednesday, August 6, 1980

Workshops Resume

8:30	Workshop A	Drs. Jenkins and Paul
	Workshop B	Drs. DeSilva and Dimsdale
	Workshop C	Drs. Herd and Verrier
12:00	Lunch - NAS Refectory	

Plenary Meeting - NAS Auditorium

1:00	Summaries from each Workshop and Discussion from the Floor	
3:00	Concluding Remarks and Adjournment	Dr. Dews

BIOBEHAVIORAL FACTORS IN SUDDEN CARDIAC DEATH

Participants

Joseph H. Autry, M.D.
Coordinator, Clinical Research Center Program
National Institute of Mental Health
Rockville, Maryland

*Eugene Braunwald, M.D.
Hersey Professor of the Theory and Practice of Physic (Medicine)
Harvard Medical School
Boston, Massachusetts

James C. Buell, M.D.
Chief of Cardiology
Omaha Veterans Administration Medical Center
Omaha, Nebraska

Caren Carney, M.A.
Research Associate
Institute of Medicine
Washington, D.C.

William Castelli, M.D.
Medical Director
Framingham Heart Study
Framingham, Massachusetts

Marilyn Cebelin, M.D.
Deputy Coroner and Associate Pathologist
Cuyahoga County Coroner's Office
Cleveland, Ohio

David Cohen, Ph.D.
Chair of Neurobiology and Behavior Department
State University of New York
Stony Brook, New York

Frances Cohen, Ph.D.
Assistant Professor of Medical Psychology
University of California School of Medicine
San Francisco, California

Louis Cohen, M.D.
Professor of Medicine (Cardiology)
University of Chicago School of Medicine
Chicago, Illinois

Theodore Dembroski, Ph.D.
Professor of Psychology
Eckert College
St. Petersburg, Florida

Regis DeSilva, M.D.
Brigham and Women's Hospital
Harvard Medical School and
Cardiovascular Laboratory, Harvard School of Public Health
Boston, Massachusetts

Peter Dews, M.B., Ch.B., Ph.D.
Stanley Cobb Professor of Psychiatry and Psychobiology
Harvard Medical School
Boston, Massachusetts

Joel Dimsdale, M.D.
Assistant Professor of Psychiatry
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

James Dingell, M.D.
Scientific Officer
National Heart, Lung and Blood Institute
Bethesda, Maryland

*Member, Institute of Medicine

Robert Eliot, M.D.
Chairman, Department of Preventive and Stress Medicine, and
Director, Cardiovascular Center
University of Nebraska Medical Center
Omaha, Nebraska

Peter L. Frommer, M.D.
Deputy Director
National Heart, Lung and Blood Institute
Bethesda, Maryland

William Greene, M.D.
Professor of Medicine and Psychiatry
University of Rochester School of Medicine and Dentistry
Rochester, New York

Thomas P. Hackett, M.D.
Chief, Psychiatry Services
Massachusetts General Hospital
Boston, Massachusetts

Jacob Haft, M.D.
Chief of Cardiology
St. Michael's Medical Center
Newark, New Jersey

James P. Henry, M.D.
Professor of Physiology and Biophysics
University of Southern California
Los Angeles, California

J. Alan Herd, M.D.
Associate Professor
New England Regional Primate Research Center
Harvard Medical School
Southborough, Massachusetts

Lawrence Hinkle, M.D.
Professor of Medicine
The New York Hospital - Cornell Medical Center
New York, New York

C. David Jenkins, Ph.D.
Director
Department of Behavioral Epidemiology
Boston University Medical Center
Boston, Massachusetts

John Lacey, Ph.D.
Senior Scientist in Psychophysiology
Fels Research Institute
Yellow Springs, Ohio

James Lawler, Ph.D.
Associate Professor of Psychology
University of Tennessee
Knoxville, Tennessee

*Robert Murray, M.D.
Senior Scholar in Residence
Institute of Medicine
Washington, D.C.

William Orr, Ph.D.
Director, Clinical Physiology
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

Oglesby Paul, M.D.
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Harold Pincus, M.D.
Special Assistant to the Director
National Institute of Mental Health
Rockville, Maryland

*Member, Institute of Medicine

David Randall, Ph.D.
Associate Professor of Physiology and Biophysics
University of Kentucky College of Medicine
Lexington, Kentucky

Peter Reich, M.D.
Chief, Psychiatry Service
Peter Bent Brigham Hospital
Boston, Massachusetts

Donald Reis, M.D.
Director, Laboratory of Neurobiology
Cornell Medical College
New York, New York

*Judith Rodin, Ph.D.
Professor of Psychology and Psychiatry
Yale University
New Haven, Connecticut

Richard S. Ross, M.D.
Vice President and Dean
Johns Hopkins University School of Medicine
Baltimore, Maryland

William Ruberman, M.D.
Director for Medical Research
Health Insurance Plan
New York, New York

Daniel D. Savage, M.D., Ph.D.
Chief, Noninvasive Laboratories
Framingham Heart Study
Farmingham, Massachusetts

Gary Schwartz, Ph.D.
Professor of Psychology and Psychiatry
Yale University
New Haven, Connecticut

Charles Spielberger, Ph.D.
Professor of Psychology
University of South Florida
Tampa, Florida

Richard L. Verrier, Ph.D.
Assistant Professor of Physiology
Harvard Medical School and
Cardiovascular Laboratory, Harvard School of Public Health
Boston, Massachusetts

Stephen Weiss, Ph.D.
Chief, Behavioral Medicine Branch
National Heart, Lung and Blood Institute
Bethesda, Maryland

Theodore Weiss, M.D.
Assistant Professor of Psychiatry
University of Pennsylvania Hospital
Philadelphia, Pennsylvania

Myrna M. Weissman, Ph.D.
Associate Professor
Department of Psychiatry
Yale University
New Haven, Connecticut

Redford Williams, M.D.
Professor of Psychiatry
Duke University Medical Center
Durham, North Carolina

*Member, Institute of Medicine

Observers

Ronald Abeles, Ph.D.
National Institute on Aging

Marsha Goldberg
Institute of Medicine

Margaret Mattson, Ph.D.
National Heart, Lung and Blood Institute

Angela Mikalide
National Heart, Lung and Blood Institute

Michelle Trudeau
Institute of Medicine

Stephen Weinstein, Ph.D.
National Heart, Lung and Blood Institute